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EFFECTS OF A FAT-FREE DIET ON THE STRUCTURE OF THE KIDNEY IN RATS*

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MINNEAPOLIS

Burr and Burr [1] produced a new deficiency disease in rats by the rigid exclusion of fat from the diet. Since bloody urine and an abnormal appearance of the kidneys were often observed, they concluded that renal disorder may be an important factor in this disease. The primary object in the present study was to determine the nature and extent of the structural changes found in the kidneys of these rats. Dr. George O. Burr allowed us to investigate this material.

MATERIAL AND METHODS

Table 1 gives the composition of the basal diets used in most cases, including casein (highly purified), sucrose and salt mixture, supplemented in some cases by lard or other fats. The fats were carefully extracted from the yeast (used for vitamin B complex). The nonsaponifiable matter of the cod liver oil ("fraction AD" for vitamins A and D) and of the wheat germ ("fraction E" for vitamin E) were used. The details concerning the diet are given in the publications by Burr and Burr.[1]

Burr and Burr found that rats reared, after weaning (at 3 weeks of age), on this fat-free diet soon begin to show a characteristic disorder. The disease is characterized externally by an abnormal, scaly condition of the skin, especially on the dorsa of the feet. This condition usually becomes apparent between the fiftieth and ninetieth day of life. The tail becomes irregularly and coarsely scaled; the tip may become inflamed and swollen, and from 1 to 3 cm. of it may become necrotic and drop off. The hair on the back is often filled with dandruff. There is a tendency for the hair to fall out, especially around the face, neck and back. Growth is subnormal and usually ceases at about 5 months of

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* From the Department of Anatomy, University of Minnesota. The work was aided by a grant from the Medical Research Fund of the University of Minnesota.

1. Burr, G. O., and Burr, M. M.: A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet, J. Biol. Chem. **82**:345, 1929; On the Nature and Rôle of the Fatty Acids Essential in Nutrition, ibid. **86**:587, 1930.

age. After a stationary period of variable length the rat loses weight rapidly and dies. Bloody urine is frequently noted in the later stages.

The cutaneous lesions in this new disease suggest pellagra. But 0.7 Gm. of whole yeast powder given daily failed to protect the rats from the disorder, and an increased dosage of yeast failed to cure. This would apparently exclude pellagra.

To test the adequacy of the extract of cod liver oil as a source of vitamins A and D, three rats were reared on the fatless diet plus 10 drops of lard daily. No extract of cod liver oil was given. In the seventh week all had xerophthalmia, and one died; whereas their controls, receiving the usual dose of the extract of cod liver oil, were growing normally with no signs of deficiency at 10 months of age. It was also found that doubling the dose of the extract of cod liver oil, or the addition of butter failed to cure sick animals on the fatless diet. The disorder therefore cannot be ascribed to any deficiency in vitamins A

TABLE 1.—*Composition of Basal Diets Used (Burr and Burr*[1]*)* *

Diet	Pure Casein, %	Sucrose, %	Salt Mixture, %	Lard, %
550	24.0	72.1	3.9	0
550A	16.0	80.1	3.9	0
550B	12.0	84.1	3.9	0
560	30.1	45.1	4.8	20
560A	20.0	55.1	4.8	20
560B	15.0	60.1	4.8	20

* Modifications and accessories used are explained in the text.

and D. The presence or absence of vitamin E in the diet likewise makes no difference in the appearance of the characteristic disorder.

When an addition of 20 per cent of lard, or even 10 drops of lard daily, was included in the diet of the young rats, comparatively good growth resulted, and no lesions of the skin and tail were present. Animals receiving even as little fat as is present in 3 drops of cod liver oil daily (when this was given for vitamins A and D instead of the concentrate of cod liver oil) remained generally healthy for a period of a year, although some abnormal scales were found on the feet and tail.

Once the disease has developed, rats can apparently be cured by the addition of 20 per cent of lard to the diet, or even by the addition of 10 drops of lard daily (2 per cent of diet). It was also found that the disease can be readily prevented or cured by the addition of 2 per cent of certain fatty acids to the diet, but the nonsaponifiable portion of fats and glycerol were ineffective for preventing or curing the disease. Apparently some necessary fats (linoleic acid and perhaps others) cannot be synthesized in the organism and must be supplied in the diet.

For the present study, the kidneys from 124 rats were available. These included a series from the animals used by Burr and Burr,[1] together with those from a

number of other rats used in more recent experiments by Burr and Jackson. The rats were partly of the Wistar albino strain and partly of the Long-Evans pied strain. The results were the same in both cases. Both male and female rats were used, but no sex differences were apparent. All the animals were reared in the colony at the Institute of Anatomy, where excellent care and housing are provided.

The test rats were on the experiment for variable periods, the average age at autopsy being 278 days. Rats 20 and 21 (table 2) were exceptionally young (from 72 to 74 days), while rats 13 to 17 and 96 to 111 were unusually old (about 19 months). All the rats were killed with chloroform, those found dead being excluded from the present study. The 124 rats used have been classified in 10 groups, depending largely on the diets used and the microscopic changes in the kidneys, as shown in table 2. In general (unless otherwise specified), the rats were placed first on diet 550, and later changed to diets 550A and 550B, since lower levels of protein suffice with advancing age. The special diets of the various groups will be given in the section on observations.

At autopsy (by C. M. Jackson) the kidneys were usually placed in 4 per cent formaldehyde. As these experiments with fatless diets have been in progress for about two years, the fixation in some cases was necessarily prolonged. Group 2 (test rats) and rats 43 to 46 in group 4 (cured rats) were preserved in formaldehyde from fifteen to seventeen months. This is unfortunate, since prolonged fixation probably changes somewhat the finer histologic structure and staining capacity. In particular, it lessens the amount of demonstrable fat, as shown by Bell [2] and others. The kidneys from the eight stock animals were fixed in formaldehyde for only from twenty-four to forty-eight hours. Kidneys from the remaining groups were fixed from one to six months. Zenker fixation was also used in a few instances.

For general histologic study, sections a few millimeters thick were embedded in paraffin, cut in sections at 5 microns and stained with hematoxylin-eosin or Mallory's aniline blue. Several other stains were also used. For a study of fat (or lipoid) content, frozen sections were made and stained with sudan III or scarlet red. Von Kossa's silver nitrate method was used for the demonstration of calcium deposits.

OBSERVATIONS

As mentioned, the 124 rats used in this study were classified into 10 groups, as shown in table 2. These include 3 groups of test rats, 2 groups of cured rats and 5 groups of control animals.

RATS USED FOR TESTS

Forty-two of the 124 rats were reared on the test (fatless) diets, and are classified in 3 groups: 1, 2 and 3.

Group 1.—As shown in table 2, group 1 included twenty-one animals. They were reared at first on basal diet 550, later on 550 A and 550 B (table 1). These diets were supplemented daily with ether-extracted yeast and "fraction AD"; and, with the exception of rats 13 to 18, they also received the wheat germ ("fraction E").

2. Bell, E. T.: On the Occurrence of Fat in the Epithelium, Cartilage, and Muscle Fibers of the Ox, Am. J. Anat. **9**:401, 1909.

TABLE 2.—*Individual Data on the Kidneys in Rats Used in the Experiments and in Normal Rats* *

Number	Calcification	Uncalcified Degeneration	Fat Content	Casts in Medulla	Hyperplasia of Pelvic Epithelium	Infiltration by Round Cells
		Group 1. Test Rats (Strictly Fatless Diet)				
1	p+++, c++	p+++, c++	p+, c+++	+f, a	++	++
2	.....	p+	p+, c+	.....	..	+
3	p+	p+, c+	p+, c+	+f	+++	++
4	p+++, c++	p+	p++, c+	+++f, a	++	+
5	c++	p+, c++	p++, c++	++f		
6	.....	p+	p+, c++	++f	..	+
7	.....	p+	p+	.....	..	++
8	c++	p++, c+	p++, c+	++f, a	++	
9	c+	p++	c+	+++f, a	+	+
10	c+	p++	p+, c+	++f, a	+	
11	c++	p++	p++, c+	+++f, a		
12	p+	p++, c+	p++, c+	+f	..	++
13	c+	p++, c+	p++, c+++	++f, a	..	+
14	p+++, c+++	p++	p+, c+	++f, a	+++	
15	p++, c++	p++, c++	p++, c+++	++f, a	+	+
16	p+, c+	p++	p++, c++	+++f	+	+
17	c+	p++	p+, c+	++f, a		
18	c+	.....	c+	+f, a		
19	p++, c+	p+, c+	p+, c+	.....	+	+
20	.....	.....	.....	.....	..	+
21	c±	.....	.....	.....	..	+
		Group 2. Test Rats (Fatless Diet Supplemented with Cod Liver Oil)				
22	.....	p+	.....	.....	..	+
23	.....	p+	.....	.....	+	
24	.....	.....	.....	.....	+	+
25	.....	.....	.....	.....	..	+
26	.....	p+				
27	.....	.....	.....	.....	..	+
28	.....	.....	.....	+f, a		
29	.....	p++, c+	p±	.....	+	
30	.....	c+	p±	.....	..	++
31	c+	c+	.....	.....	+	++
32						
33	c+	p++, c+	p+	.....	..	+
		Group 3. Test Rats (Fatless Diet Supplemented with Various Ineffective Fats)				
34	c++	p+	.....	.....	..	+
35	c++	p+	p+, c+	.....	..	+
36	c++	p+, c++	p++, c++	a		
37	c+	c+	p+, c++	+f	..	+
38	c++	p+, c+	p+, c+++	+f	..	+
39	p++, c+++	p++, c+	.....	a	+	+
40	c++	p+, c±	p++, c+++	+f, a		
41	c+++	c+	.....	.....	..	+
42	c+					
		Group 4. Cured Rats (Strictly Fatless Diet; Later Cured by Adding 2 to 20 per Cent of Lard)				
43	.....	p+				
44	.....	p+	.....	.....	..	+
45	.....	.....	.....	.....	..	+
46	.....	p+, c+	.....	.....	..	+
47	.....	c±	p+			
48	.....	.....	p+	.....	..	+++
49	.....	.....	c+	+++f, a	..	+
50	p±	.....	.....	.....	+	
51	.....	.....	p+, c+	++f	..	+
		Group 5. Cured Rats (Fatless Diet; Cured by Adding Fat in Various Forms)				
52	c+++	p++, c+	p+, c+	+f	..	+
53	p+	p++	p+, c+	+f, a	+	
54	p+, c+	c+	c+	+f	++	+
55	c+++	p++, c+	p+, c+			
56	c+	p+, c+	p+	+a	..	++
57	c+++	p+, c++	p++, c+	++f, +a	..	+
58	c+	c+	p++, c++	+f	..	+
59	c+	p+, c+	p+, c++	++f	..	+
60	.....	p+	p+, c+	+f	..	+
61	.....	.....	c+	.....	..	+
62	c+++	p+, c+	c+	.....	..	±
63	c++	c+	p+, c+	.....	..	+
64	.....	p+	c+	+a	..	+

* Location of lesions designated by p, papillary region (medulla); c, cortical tubules. Casts are designated as f (fatty), a (albuminous) or c (calcified). The sign ± indicates merely traces, while +, ++ or +++ represent slight amount, moderate amount or abundance, of the corresponding character.

TABLE 2.—*Individual Data on the Kidneys in Rats Used in the Experiments and in Normal Rats*—Continued*

Number	Calcification	Uncalcified Degeneration	Fat Content	Casts in Medulla	Hyperplasia of Pelvic Epithelium	Infiltration by Round Cells
		Group 5. Continued				
65	.....	.....	p++, e+++	+f	..	+
66	.....	.....	p++, e++	.....	..	+
67	p+, e±	.....	p+, e++	.....	+	+
68	p+, e+	p+, e±	p+	++e		
69	p+, e++	p+, e+	p+, e+	+e	+	+
70	e±	p+	p+, e+++	++f	..	++
71	e+++	e++	p++, e+			
72	p±, e+	p+	.....	.....	+	+
73	e+	p+	e+	.....	..	++
74	e++	e+	p+, e+	.....	..	+
75	e++	.....	.....	.....	..	+
76	e+++	e±	p+, e+	+f	..	+
77	.....	p+	p+, e+			
78	e++	p+, e+	e+++	.....	..	+
79	e+++	.....	p+, e+	++f	..	++(?)
80	e±	p±	.....	.....	..	+
81	.....	e+	p++, e+	.....	..	+++
82	p+	p++	e+	.....	++	++
83	e++	.....	p+, e+	++f, e	..	++
84	e+	p+	p+, e+	+f	..	+
85	e++	p+, e+	p+, . e+			
86	e++	p±, e+	p+	a	..	+
		Group 6. Control Rats (Fatless Diet Plus 10 Drops of Lard Daily)				
87	.....	.....	p±			
88	.....	p+	p+	.....	..	+
89	.....	p+	p+			
90	.....	.....	p±, e±	.....	..	+
91						
92						
93	.....	.....	p+	.....	..	+
94	e±	.....	p+	.....	..	+
95	.....	e+	.....	.....	..	+
		Group 7. Control Rats (20 per Cent of Lard in the Diet)				
96	.....	e++	e+			
97	.....	p+	p++, e+	+f	..	+
98	.....	e++	p+, e+	.....	..	+
99	.....	e++	p±			
100	.....	.....	p+, e±	+f, a		
101	.....	p+, e+	p++, e+	+f, a	..	++
102	.....	p+, e+	p++, e+			
		Group 8. Control Rats (Fatless Diet Plus Various Kinds of Fat Daily)				
103	.....	e++	p+, e+	++f, a	..	+
104	.....	p+, e+	p+			
105	.....	.....	.....	.....	..	+
106	.....	.....	p±, e±			
107	.....	.....	e±	.....	..	+
108	.....	p+	p+, e+			
109	e+	e+	p±, e±			
110	e+	p+	p+, e+	+f	+	+
111	.....	p+	p±	.....	..	+
		Group 9. Normal Rats (Diet Containing Starch)				
112	.....	p±	p±	.....	..	+
113	.....	p±	p±	.....	..	+
114	.....	.....	p±	.....	..	+
115	.....	.....	p±			
116	.....	p+	p+	.....	..	+
		Group 10. Normal Rats (Stock Diet)				
117	.....	.....	p±	.....	..	+
118	.....	.....	p±	.....	..	+
119	.....	.....	p±	.....	..	+
120	.....	.....	p±	.....	..	+
121	.....	.....	.....	.....	..	+
122	.....	.....	p±	.....	..	+
123	.....	.....	.....	.....	..	+
124						

With three exceptions, the rats of this group exhibited varying degrees of poor nutrition at autopsy. Emaciation was most marked in the oldest rats (13 to 17 inclusive). The tail was coarsely scaled in every case, and the coat of hair thin and rough. For the whole group, the body weight averaged 26.8 per cent below the Wistar norm [3] (for corresponding body length), the range being from 7 to 41 per cent.

Grossly, the kidneys usually appeared large and pale. The surface varied somewhat, that of some of the organs being finely pitted, while that of others was coarsely granular and sometimes sprinkled with small, whitish specks. Very fine pitting apparently occurs sometimes in normal kidneys, a circumstance which may be a source of confusion. The kidneys of the rats in this group averaged 21.8 per cent above the Wistar norm for weight according to body length, ranging from 18 per cent below to 105 per cent above normal.

Microscopically, variations from the normal controls appeared in the cortex, the medulla and the pelvis. They will be described in this order. The distribution of the lesions is shown in table 2.

Cortex: In sections of the cortex, the lesions noted were restricted chiefly to the tubules, the glomeruli showing no definite changes. The most striking and characteristic lesion in this region was the appearance, in certain isolated tubules, of cells that stained a deep blue with hematoxylin and black with von Kossa's stain, indicating the deposition of calcium. Usually the lumen of each of these tubules contained a certain amount of débris, which was also calcified, so that in cross-section the usual appearance was that of a large calcareous cast surrounded by the basement membrane alone, the cells having partially disintegrated (fig. 1). In a few cases, the deposits appeared merely as fine cytoplasmic granules in the cells of the tubules. In such cases the nucleus sometimes appeared uncalcified. But when more dense calcification had taken place, the cells fused, and the nuclei were not visible.

These calcified tubules occurred singly and were usually found near the corticomedullary border, although they were not necessarily limited to this region. The process in general was degenerative (a "nephrosis"), since usually no appearance of associated inflammation was noted. There was some evidence that this calcification might have been preceded by fatty degeneration and desquamation of tubular epithelium. However, the tubular cells immediately adjacent to the calcified tubules and the cells throughout the remainder of the cortex, except in these few isolated tubules, were usually normal in appearance.

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3. Donaldson, H. H.: The Rat (ed. 2), Memoirs of the Wistar Institute of Anatomy, Philadelphia, Wistar Institute, 1924.

Calcification of cortical tubules was demonstrated in fifteen of the twenty-one kidneys in this group (table 2). A typical section across the kidney presented from three to ten strongly calcified tubules arranged near the corticomedullary border. In a few cases, however, various stages of cellular degeneration appeared over the entire cortex, and in some of these calcification was more widespread.

Rats 20 and 21 were killed at the age of 74 and 72 days, respectively, having been on the fatless diet only about seven weeks. They demonstrated merely some of the earliest manifestations of the resulting disorder. The external appearance of both was normal, except for a slight abnormal scaliness of the dorsa of the feet and the tip of the tail.

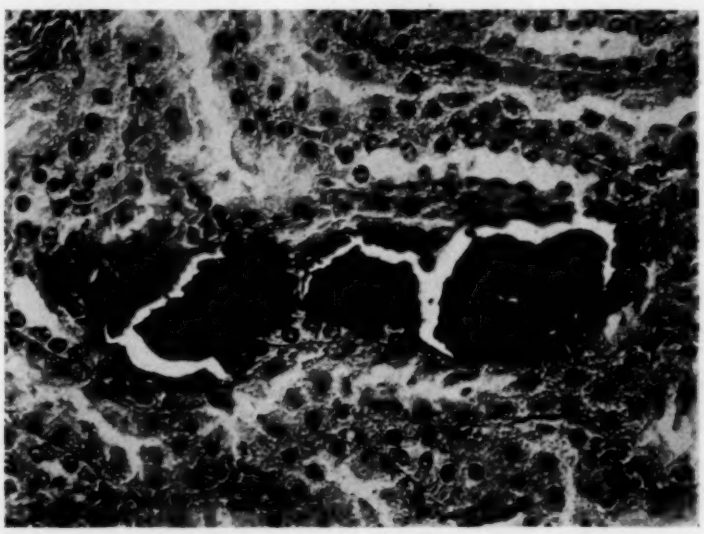

Fig. 1.—Photograph of a section of the kidney from test rat 11, showing calcification in a cortical tubule. Hematoxylin-eosin stain; × 330.

Grossly, the kidneys were normal, except for enlargement. Microscopically, aside from a small amount of infiltration by round cells in both, the only lesion was a slight calcification in some of the cortical tubules in rat 21.

As mentioned, uncalcified degeneration also sometimes occurred in the cortical tubular epithelium. When present (fig. 2), it appeared, as a rule, throughout the cortex. The cytoplasm in the degenerating epithelium stained less readily, became fragmented and sloughed off into the lumen of the tubule. The nuclei showed various stages of pyknosis and karyolysis. This type of widespread cellular degeneration was noted in eight of the twenty-one kidneys in this test group. It might have been related to the general condition of the animal, since many of these

rats were emaciated at autopsy. The picture closely resembles that shown by Jackson [4] for typical renal degeneration during severe inanition.

In cases in which the cytoplasm of the degenerating cells was not entirely disintegrated, frozen sections stained with sudan III showed an apparent increase in intracellular fat (or lipoid). This fat appeared as small and medium-sized droplets, either in the basal portion of the cell or throughout the cytoplasm. Both proximal and distal convoluted tubules and the ascending limb of Henle's loop occasionally showed this fatty change. In some cases, the fatty condition of the tubules was widespread throughout the entire cortex. At other times it was

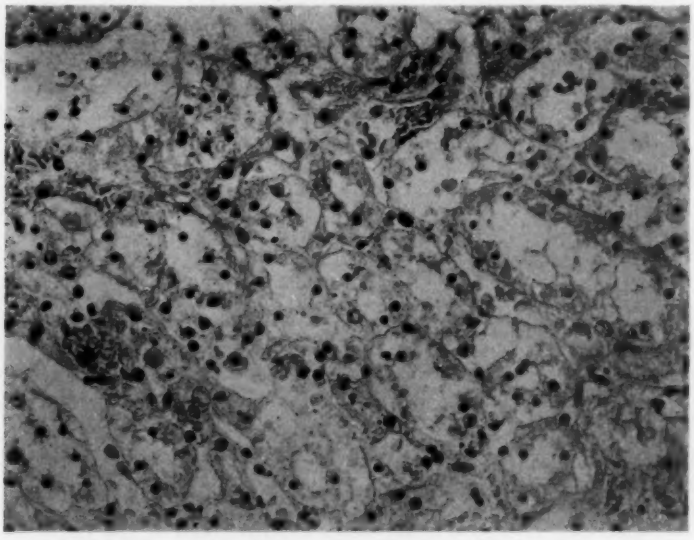

Fig. 2.—Photomicrograph of a section of the renal cortex from test rat 29, showing the typical uncalcified cortical tubular degeneration. Hematoxylin-eosin stain; × 300.

apparent in isolated groups of tubules only, and then the individual cells usually showed only a moderate amount. From table 2 it can be seen that group 1 of the test rats nearly all showed more or less fat in the cells of the cortical tubules.

The occurrence of demonstrable fat where there was no obvious appearance of degeneration would seem to indicate that fat is normally present in the tubular epithelium. It may be possible, however, that the appearance of fat in the renal cells was merely the first indication of

4. Jackson, C. M.: The Effects of Inanition and Malnutrition on Growth and Structure, Philadelphia, P. Blakiston's Son & Company, 1925.

degenerative change, since the kidneys of normal stock animals showed no fat in these cells. This question will be considered later under "Comment and Conclusions." Associated with this fatty metamorphosis of the cortical tubules were certain fatty casts in the medulla, which will be described later.

Focal points of round cell (lymphocytic) infiltration were observed in fourteen of the twenty-one kidneys of this group. The groups of round cells occurred around some of the small arteries and between the tubules. A typical section of the entire kidney showed from four to six such areas. This was probably indicative of some sort of a chronic inflammatory process, but since it was found also in the kidneys of normal stock animals, it was not characteristic of the fat-deficiency disease.

In a few cases, an inflammation of low grade apparently involved also the renal epithelium, small areas being present where the tubules were shrunken and their outlines obliterated, with an associated infiltration by round cells and an increase in connective tissue fibers. No definite changes were noted in the glomeruli. No polymorphonuclear leukocytes indicating acute inflammation were found. These shrunken areas, when near the renal surface, accounted for the gross appearance of a coarsely pitted surface, but the finely pitted or granular areas frequently noted at autopsy could not be correlated with any microscopic lesions.

In several cases, a dilation of some of the cortical tubules was noted. This appeared mainly in the larger collecting tubules, and was possibly due to some obstruction to the flow of urine in the papillary ducts. Somewhat similar, but more extensive, lesions representing spontaneous interstitial nephritis have frequently been observed in rats and other laboratory animals (Jackson [5]).

Medulla: In this group (on strictly fatless diet), the lesions shown in sections of the medulla were often restricted to the cells of the papillary ducts. In comparison with those of normal controls, the boundaries of the cells in the degenerative regions appeared indistinct, the cytoplasm atrophic and sometimes vacuolated, and the nuclei pale, with a deeply staining nuclear membrane.

Frozen sections stained with sudan III often showed in these degenerative areas many fine droplets of fat (or lipoid) in the epithelial cells of the medullary ducts and also in the adjacent interstitial tissue. In other cases, the lumina of the ducts were filled with many small fat droplets. These formed large, elongated cylindric casts (fig. 3). Often

5. Jackson, C. M.: Spontaneous Nephritis and Compensatory Renal Hypertrophy in Albino Rats on Diet Deficient in Vitamin A, Proc. Soc. Exper. Biol. & Med. **22**:410, 1925.

this fatty material in the lumen was intermingled with a homogeneous substance that stained pale blue with hematoxylin, and may have been precipitated albumin. These fatty casts appeared more numerous when the fatty change in the cortical tubules was most pronounced. They were possibly due in part to fat droplets which had escaped into the lumina of the corresponding convoluted tubules and later had passed down into the ducts of the medulla, where they appeared as casts.

In the extreme cases (rats 1, 3, 4, 12, 14, 15 and 16), the renal papilla appeared largely necrotic and much of it might be sloughed off into the pelvis (fig. 4). In these cases, irregular masses of the necrotic material stained a deep blue with hematoxylin and black with von

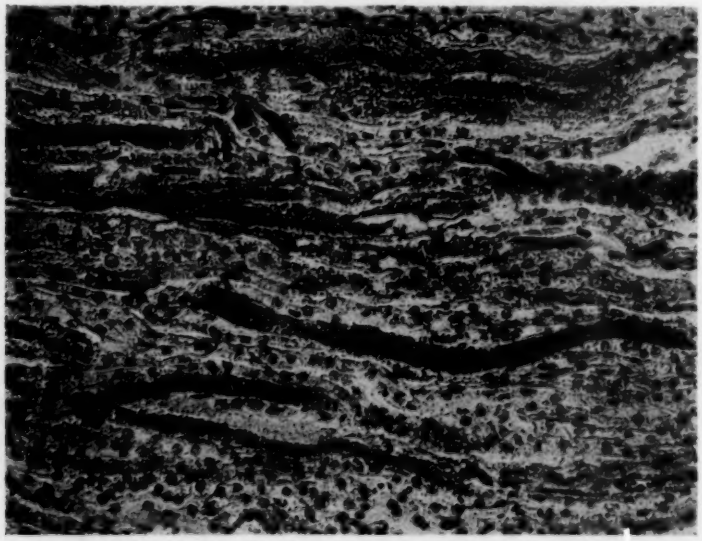

Fig. 3.—Photomicrograph of a longitudinal section of the renal medulla from test rat 4, showing fatty casts in the ducts. Sudan III stain; × 180.

Kossa's stain, indicating that here in the medulla (as in the cortex) calcification had taken place. Higher up in the pyramid in such cases casts of fatty-albuminous material sometimes appeared in the lumina of the degenerating ducts; and, as the necrotic area was approached, this material, as well as the degenerating tissue, became intermingled with the deposits of calcium. The appearance of the calcification in a cross-section of the renal papilla is shown in figure 5.

This picture of necrosis and calcification in the papilla was present in eight of the twenty-one kidneys in this group. In two of the eight, bacteria and a few polymorphonuclear leukocytes were present in the necrotic area. These, however, apparently represented superimposed

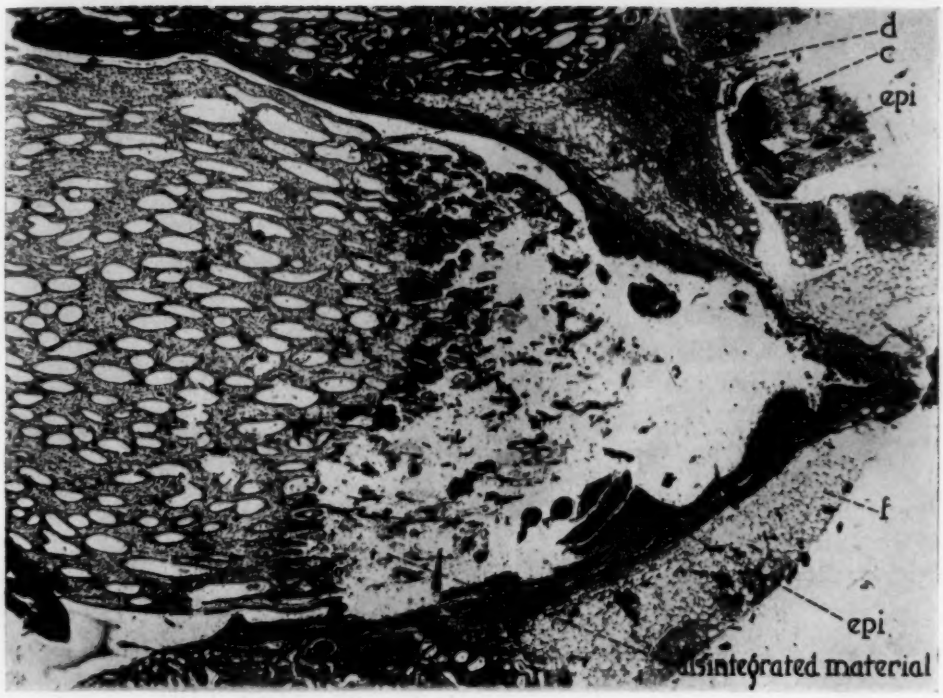

Fig. 4.—Photomicrograph of a section of the kidney from test rat 3, showing necrosis, apical disintegration and calcification in the papilla; also hyperplasia of the pelvic epithelium. Hematoxylin-eosin stain; × 27. The letters indicate, *d*, papillary duct; *c*, calcification; *epi*, proliferated pelvic epithelium, and *f*, perirenal fat.

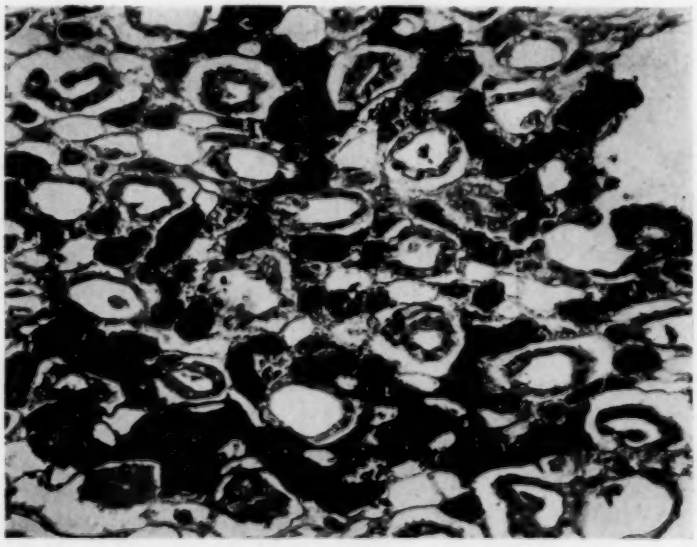

Fig. 5.—Photomicrograph of a cross-section of the renal papilla from test rat 16, showing areas of calcification (black). Hematoxylin-eosin stain; × 150.

infections, since in the remaining kidneys no evidence of inflammatory reaction could be found.

Renal Pelvis: In ten of twenty-one kidneys of this group (on strictly fatless diets), a proliferation of the pelvic epithelium was noted. This epithelium, which is normally of a low transitional type, became hyperplastic and greatly thickened in certain regions. This sometimes gave the impression of a very small papilloma with a broad base (fig. 4). No evidence of epithelial cornification was present. These hyperplastic areas were most marked where necrosis was present in the adjacent tip of the renal papilla.

In several cases in which the papilla was intact, the surface epithelium lining it, although not proliferated, showed some fine irregular droplets of fat in the cells. The hyperplastic pelvic epithelium contained no fatty material, however.

Group 2.—As shown in table 2, this group included twelve test rats. Five of these (rats 23, 24, 26, 27 and 28) were kept throughout on the diet high in protein (24 per cent)—diet 550; the others were changed as usual from 550 to 550 A and 550 B. A daily supplement of "fraction AD" was given, but later a change was made to 2 drops of cod liver oil. The yeast and wheat germ supplements were also unmodified in some cases. This dietary experiment therefore constituted a modified test, since some fat was present in the cod liver oil, the ordinary yeast (which contains 1.5 per cent fat), and the wheat germ (which contains 10 per cent fat). Moreover, rat 18 had been partially cured by the addition of from 5 to 15 drops of coconut oil to the diet daily.

This group presented differences from group 1, the manifestations of the disease being, in general, much less pronounced. The average body weight was only 8.6 per cent below the Wistar norm; range, 9 per cent above to 26 per cent below. Poor general nutrition was noted in only one case. The remaining eleven were either normal or nearly so as regards the general condition of the body. More or less typical lesions of the tail, however, were present in every case, except one.

The kidneys of this group were large, but entirely normal in surface appearance. They averaged 25 per cent heavier than the Wistar norm; range, from 11 per cent below to 58 per cent above normal.

Microscopically, the kidneys of group 2 showed much less severe lesions than those of group 1, as shown clearly in table 2. Calcification of the cortical tubules was present in only two cases. Cortical tubular degeneration was present in four rats, but in no case was any fatty material found in the cortex. However, this lack of fat means little, since the kidneys of this group were fixed in formaldehyde for from fifteen to seventeen months.

Infiltration by round cells occurred with about the same frequency as in group 1. The small atrophic areas that were responsible for the coarse pits in the surfaces of the kidneys of group 1 were not present in group 2. This was in accordance with the normal appearance of the surface in the kidneys of this group.

In five of the twelve kidneys of group 2, a slight or moderate degeneration of the epithelial cells in the papillary ducts was noted. None of these showed necrosis or calcification. Fat (or lipoid) was demonstrable in this region in only three cases, as a few scattered droplets in the cells of the papillary ducts and interstitial tissue. Here again, however, the lack of fat may have been due to long preservation in formaldehyde. In one case only, a few "albuminous" casts were present in some small ducts in the upper part of the pyramid.

A slight proliferation of pelvic epithelium was indicated in four cases of this group.

Group 3.—As shown in table 2, this group included nine test rats. They were reared throughout on diet 550 B (low in protein), supplemented with "fraction AD," extracted yeast and wheat germ ("fraction E"). In this group, cures were attempted with various fats (hydrogenated coconut oil, liver lipoids, methyl oleate, butter fat), but these failed to restore normal body weight and general external appearance. Therefore the results in this group may be considered as those of a modified test.

In general condition the rats in this group closely resembled those of group 1. All exhibited poor nutrition at autopsy, and characteristic lesions of the skin were present in every case. Body weight in this group averaged 27 (range, from 15 to 31) per cent below the Wistar norm.

Microscopically (table 2, group 3), certain cortical tubules presented distinct and characteristic calcification in every case. Likewise, the other lesions, in general, agreed closely with those of group 1. Hyperplasia of the pelvic epithelium, however, occurred in only one case. Calcification was present in the papilla only once, and in that case little apical necrosis appeared.

CURED RATS

Forty-four rats were apparently cured of the disease (with regard to body weight and cutaneous lesions) by the addition of varying amounts and types of fat to the diet. These cured rats are divided into two groups, 4 and 5.

Group 4.—As shown in table 2, group 4 included nine rats. Rats 47 to 51 were reared on diet 550 B, low in protein and fatless; rats 43 to 46, as usual, on diet 550, and later, on 550 A and 550 B. All these

diets were supplemented daily with extracted yeast, "fraction AD" and wheat germ ("fraction E"). Rats 43 and 44 received daily the alcoholic extract of 1 Gm. of fresh placenta. Later a cure was obtained in rats 43 to 46 by changing them to diet 560 (containing 20 per cent of lard), and in rats 47 to 51 by the daily addition to their food of from 10 to 15 drops of lard (from 2 to 3 per cent of the diet).

As shown by the records, the cutaneous lesions in this group disappeared, and body weight (which had become nearly stationary) increased rapidly. At autopsy, these rats were in excellent condition, with the exception of a slight abnormal scaliness of the tip of the tail in rat 46. Body weight was practically normal, averaging only 4 per cent below the Wistar norm for length.

The kidneys of this group at autopsy appeared normal grossly, and in weight averaged 1.2 per cent above the Wistar norm; range, from 8 per cent below to 12 per cent above.

Histologically, the kidneys of this group usually showed little difference from those of the normal controls. In three cases, however, the cells of the papillary ducts showed slight degeneration. In two cases, the cortical tubules also appeared somewhat degenerated. However, none showed the more severe lesions, such as necrosis and calcification, except very slight calcification in the papilla of rat 50. Infiltration by round cell was noted in six of the nine cases in this group. The absence of demonstrable cortical fat in rats 43 to 46 may again have been due to preservation for about seventeen months in formaldehyde.

Group 5.—In general, the thirty-five rats in group 5 appeared normal as regards external condition. But since the cures were all apparently ineffective, so far as the renal lesions were concerned, these rats were grouped separately. The first six rats in this group were reared at first on fatless diet 550, later being transferred to diets 550 A and 550 B. The others of this group were reared throughout on diet 550 B, low in protein. All the diets were supplemented with "fraction AD," yeast and (usually) wheat germ ("fraction E"). After the typical external symptoms had appeared, these rats were (apparently) cured by the addition of small amounts (usually 5 drops daily) of fat in various forms. These included linseed oil, corn oil, olive oil, egg lecithin, methyl stearate, methyl linolate and poppy seed oil.

Rats 82 to 86, inclusive, constituted a group of "late cures," since they were kept on the test diet for a relatively longer period than the other cured animals. These late cures were achieved by the addition of 10 drops of corn oil to the diet daily.

At autopsy, the general condition of group 5 was good or fair. With the exception of a slight abnormal scaling of the tail in rats 67,

82 and 85 and a slight roughening of the coat of hair in rats 54, 63 and 64, no lesions of the skin were present. The average body weight of this group was 10.2 per cent below the Wistar norm; range, 18 above to 29 per cent below.

However, these supposedly cured rats showed in histologic preparations rather striking lesions of the kidneys, as is evident in table 2. Calcification of the cortical tubules was present to a variable extent in twenty-six of the thirty-five rats in this group. Uncalcified degeneration in the cortical tubules was frequent, but not severe in any case. An increase in intracellular fat (or lipoid) in these cells was nearly constant. Infiltration by round cells was present to about the same extent as previously described for other groups.

Degeneration of cells of the papillary ducts was present in twenty-one of the thirty-five cases, with calcification and necrosis in the papilla in seven of the twenty-one. The necrotic areas, however, were always relatively small, and never so extensive as those in group 1 (fig. 4). An increase of fat (or lipoid) appeared in the cells and lumina of these ducts.

Hyperplasia of pelvic epithelium was present (usually slight) in six of the thirty-five cases.

CONTROL RATS

Thirty-eight rats were available in this study as controls for the experiments with fatless diets. Of these, three groups (6, 7 and 8) were reared on the test (basal fatless) diets with the addition of various kinds and amounts of fat as preventives. Additional controls were provided by five rats (group 9) on a normal diet containing starch (no. 560 substituting starch for sucrose), and by eight rats (group 10) on the normal diet of the stock colony. Since groups 7 and 8 were obviously abnormal in general condition, the normal controls for this study included merely groups 6, 9 and 10.

Group 6.—This normal control group consisted of nine rats. Of these, rats 87 to 90 were reared on diet 550, later on 550 A and 550 B. The remaining rats (91 to 95) were kept throughout on the diet low in protein, 550 B. All received the normal supplements of "fraction AD," yeast, wheat germ ("fraction E") and 10 drops of lard daily. Externally these rats appeared normal in every way. Body weight was nearly normal, averaging only 5.3 per cent below the Wistar norm. The range was from 6 per cent above to 13 per cent below normal.

The kidneys of this group appeared normal grossly. They averaged in weight 1.5 per cent above the Wistar norm, ranging from 3 per cent below to 14 per cent above normal.

Microscopically, also, the kidneys of this group were nearly normal (table 2). The cortex was normal in all respects as compared with that of normal stock animals, with the exception of a very slight appearance of calcification in rat 94. Infiltration by round cells was present in five of the nine cases. In two cases a slight appearance of (uncalcified) degeneration was noted in the cells of the papillary ducts. In four cases an apparent increase in intracellular fat (or lipoid) was noted, and in two other cases a few scattered fat droplets (probably normal) were present in the lower portion of the pyramid.

Group 7.—The seven rats of group 7 were reared on diet 560 (20 per cent lard), supplemented by normal amounts of vitamins. It is worthy of note that the rats in groups 7 and 8 of the controls were approximately twice as old as most of the rats in the other groups.

In external appearance, the rats of this group, although not entirely normal, were not markedly abnormal. As a whole, nutrition was fair. The skin frequently appeared abnormal, although the lesions typical of the disorder caused by the fatless diet did not occur. Body weight averaged 14.4 per cent below the Wistar norm, ranging from 11 to 19 per cent below. The kidneys usually appeared grossly normal; in weight they averaged 4 per cent above the Wistar norm, ranging from 8 per cent below to 30 per cent above.

In sections of the cortex in this group (table 2) no calcification was found, but the renal tubules showed more or less degeneration in five of the seven cases, with an apparent increase in intracellular fat (or lipoid). Infiltration by round cells was noted in three of the seven cases.

In this group and in group 8 of the controls (also in rat 79), a peculiar condition was noted that was not present in the other groups. Yellowish-brown inclusion bodies were found in many of the cells of the convoluted tubules. These bodies varied in size from about half to about twice the size of the nucleus, the larger size being more common. The larger bodies were circular in outline, whereas the smaller ones were more irregular. Sometimes several of the smaller bodies could be found in a single cell. When present, they were found widespread over the entire cortex. In five of the seven kidneys of group 7, these inclusion bodies were found, and in four of these, cortical tubular degeneration was noted. The cells in which they were found, however, were not severely degenerated. They were also present in unstained sections. Since these groups of rats were much older than most of the others, it is possible that these inclusion bodies may have been related to the pigmentary degeneration occasionally described as occurring in aged individuals.

The cells of the papillary ducts appeared degenerated in three of the seven rats in group 7. An increase in fat (or lipoid) content of these cells was noted in six cases. No necrosis or calcification was found in the papillary region. Fatty-albuminous casts appeared in the medullary ducts in three cases.

Group 8.—Group 8 consisted of nine rats reared on diet 550 (changed later to 550 A and 550 B), with the usual supplements of yeast and "fraction AD," plus fat in various forms (mostly 10 drops of lard or of olive oil, or 1 Gm. of fresh liver daily). The last two rats (110 and 111) received a varied treatment, and are not strictly comparable with the others of this group.

The body weight of this group averaged 18.5 per cent below the Wistar norm, ranging from 3 per cent above to 35 per cent below. Nutrition was distinctly poor in rats 103 to 107 inclusive, but good in rats 108 and 109.

Histologically, in sections of the cortex in this group uncalcified degeneration of cortical tubular cells appeared in three of the nine cases and calcification in two cases. An apparent slight increase in intracellular fat (or lipoid) in the cortical region was noted in three cases, with traces (normal ?) in three others. The inclusion bodies described for group 7 were found in three cases. Slight infiltration by round cells was present, as found in groups previously described.

In the papillary region of the medulla, fatty (or lipoidal) material was present in seven of the nine rats in this group, three presenting the normal traces only. Uncalcified degeneration of cells of the papillary ducts was noted in four cases. Necrosis and calcification of the papilla did not occur in any of this group. Two cases showed the fatty-albuminous casts in some of the smaller medullary ducts.

In one case a typical hyperplasia of the pelvic epithelium was present.

Group 9, on Diet Containing Starch.—This group of five rats was reared on essentially the same type of normal diet as group 6, except that corn starch was substituted for sucrose.

Normal external appearance was noted in every rat of this group. The body weight averaged 3 per cent below the Wistar norm, ranging from 8 per cent below to 4 per cent above normal.

Sections showed nothing abnormal in the renal cortex, with the exception of the usual slight infiltration by round cells, which appeared in four of the five rats in this group. In the pyramid, a slight amount of epithelial degeneration appeared in the papillary ducts in one case, and little in two others. In four cases, a small amount of fat (or lipoid) was found in the pyramid, in the form of a few scattered droplets, some appearing in the epithelial cells and some in the interstitial tissue.

Group 10, on the Stock Diet.—For additional normal controls, eight rats were taken from the normal stock colony. The diet used for maintenance of this colony was McCollum's diet I, composed of ground whole wheat 67.5 (parts by weight), casein 15, whole milk powder 10, butter fat 5.2, calcium carbonate 1.5 and sodium carbonate 0.8. In this group of normal rats, the body weight averaged 7 per cent above the Wistar norm, ranging from 13 per cent above to 8 per cent below normal.

In general, the kidneys in this group appeared histologically normal (table 2). Sections showed the usual slight infiltration by round cells in every case but one. In only five of the eight cases were slight amounts of fatty material found in the papilla and lower portion of the pyramid, but none in the cortex.

COMMENT AND CONCLUSIONS

RENAL INVOLVEMENT IN THE FAT-DEFICIENCY DISORDER

In the literature, mention of lesions of the kidneys is rarely made by the workers with fat-free diets, since complete autopsies on experimental animals have rarely been made. In most cases the diets actually contained small, but appreciable, amounts of fat. In the experiments of McAmis, Anderson and Mendel,[6] however, the diets were sufficiently low in fats to give evidence of renal involvement, which was likewise noted by Burr and Burr.[1] These workers suspected that renal disorder is an important factor in the disease. This view is fully confirmed by the microscopic lesions found in the present study.

McAmis, Anderson and Mendel[6] also (contrary to the observations in the present experiments) reported urinary calculi in three rats, but these three had been previously depleted of their store of vitamin A. A deficiency of this vitamin is known to produce urinary calculi (Van Leersum,[7] McCarrison[8]). In the test rats of the present experiments, calcareofatty casts somewhat similar to those described by Van Leersum were found in the tubules of the kidneys, but they did not in any case result in vesical calculi.

Drummond and Coward[9] obtained only normal conditions in rats on diets which they considered "devoid of true fats." They also made

6. McAmis, A. J.; Anderson, W. E., and Mendel, L. B.: Growth of Rats on "Fat-Free" Diets, J. Biol. Chem. **82**:247, 1929.

7. Van Leersum, E. C.: Vitamin A Deficiency and Urolithiasis, J. Biol. Chem. **76**:137, 1928; **79**:461, 1928.

8. McCarrison, R.: The Experimental Production of Stone in the Bladder, Brit. M. J. **1**:717, 1927; Indian J. M. Research **15**:197, 1927.

9. Drummond, J. C., and Coward, K. H.: Nutrition and Growth on Diets Devoid of True Fats, Lancet **2**:698, 1921.

some autopsies, but reported no abnormal results. Their experiments, however, were continued for a relatively short period of time. Moreover, their diets were not strictly fat-free, since starch (which contains some nonextractable fat) was used in the diet, and the yeast (likewise fat-containing) was not extracted. In these experiments, as in those of Palmer and Kennedy [10] and the earlier studies of Osborne and Mendel,[11] it is probable that the negative results were due chiefly to the small, but effective, amounts of fat contained in their diets.

OCCURRENCE OF RENAL FAT

We may conclude from the work of Traina,[12] Bell,[2] Smith [13] and MacNider [14] that fatty material can be demonstrated in normal renal epithelium, but the amount apparently varies greatly with species and age, and under different physiologic and pathologic conditions.

The results of the present study agree rather closely with those of Smith [13] for normal rats. The kidneys of our normal control rats (stock animals, starch-fed rats and control group 6) showed practically no stainable fat (or lipoid), except a few scattered droplets in the medulla. These droplets appeared both in the epithelial cells and in the interstitial tissue. Our test groups (except in cases with prolonged preservation in formaldehyde) usually showed considerable quantities of fat in the cells of both medulla and cortex; and this fat appeared to be associated in some degree with degenerative changes in the cells. In the abnormal controls (groups 7 and 8), fat was also demonstrable in the cortical cells, but was much less pronounced and more variable than in the test groups. In some of these cases no appearances of cellular degeneration were present. The appearance of fat in these cells may have represented the first indication of degeneration, or it may merely have represented a different "physiologic state" which was not present in the normal controls.

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10. Palmer, L. S., and Kennedy, C.: Fundamental Food Requirements for Growth of Rat: V. Influence of Fat in Diet, Proc. Soc. Exper. Biol. & Med. **26**:427, 1929.

11. Osborne, T. B., and Mendel, L. B.: Growth on Diets Poor in True Fats, J. Biol. Chem. **45**:145, 1920.

12. Traina, R.: Ueber das Verhalten des Fettes und der Zellgranula bei chronischem Marasmus und akuten Hungerszuständen, Beitr. z. path. Anat. u. z. allg. Path. **35**:1, 1904.

13. Smith, C.: Lipoid Content of Kidney Tubule, Am. J. Anat. **27**:69, 1920.

14. MacNider, W. de B.: Concerning the Amount and Distribution of Stainable Lipoid Material in Renal Epithelium in Normal and Acutely Nephropathic Animals, with Observations on Functional Responses of the Kidney, Proc. Soc. Exper. Biol. & Med. **19**:222, 1922.

CALCIFICATION AND OTHER DEGENERATIVE CHANGES

The description by Hueper [15] of renal tubular degeneration, with subsequent calcification (due to hypercalcemia), agrees rather closely with the condition noted in the present study. In our series, however, there was no definite evidence that degenerative changes in the cortical cells always preceded calcification; but in the papillary region calcification appeared more definitely to follow cellular degeneration.

The calcium deposits in renal epithelial tubules described by Van Leersum [7] (in vitamin A deficiency) also closely resemble those noted in the present study.

Pugh [16] stated that in man the renal papillae may contain deposits of calcium in advanced age. In our study, however, age apparently is not an important factor in the process of calcification, since among the oldest animals of the entire series (groups 7 and 8 of the controls) no calcium deposits were found.

PROLIFERATION OF RENAL PELVIC EPITHELIUM

It is difficult to account for the proliferation of pelvic epithelium noted in many of the test animals. It is often associated with necrosis and calcification of the papilla (though not necessarily so), and may therefore be due in part to an irritative action of the necrotic mass in the renal pelvis.

In young rats that had died with xerophthalmia on diets deficient in vitamin A, Frontali [17] observed that all showed a variable degree of cystitis, with metaplasia of the epidermic type, involving also the ureter and renal pelvis. Cystitis was never observed in our cases, nor was an acute inflammation noted elsewhere in the kidney, except in the two cases mentioned. In these two instances, the infection was probably superimposed, since it was not found in the remaining cases.

Fujimaki and associates [18] similarly found atypical metaplasia with keratosis in the urinary bladder and renal pelvis in rats suffering from a chronic deficiency of vitamin A. Renal calculi or metaplasia (keratinization) of the pelvic epithelium were likewise found by Wolbach and

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15. Hueper, W.: Metastatic Calcification in Organs of Dog After Injections of Parathyroid Extract, Arch. Path. **3**:14, 1927.

16. Pugh, W. S.: Calcification in Kidney, Internat. J. Med. & Surg. **40**:288, 1927.

17. Frontali, G.: Infezione delle vie urinarie in carenza di vitamina A, Riv. di chir. pediat. **24**:505, 1926.

18. Fujimaki, Y.; Kimura, T.; Wada, Y., and Shimada, S.: Morphologic Changes of Pavement Epithelium of Albino Rats Fed on Vitamin A Deficient Diet, Sei-I-Kwai M. J. **46**:1, 1927.

Howe [19] and by Tyson and Smith [20] in rats and guinea-pigs with vitamin A deficiency. In our experiments, however, no indication of cornification was found in the regions of proliferated epithelium. The epithelial hyperplasia noted in our series therefore appears to be different from the metaplasia (keratosis) produced by a deficiency of vitamin A.

EFFECT OF AMOUNT OF PROTEIN IN THE DIET

The various histologic lesions observed cannot be attributed to a diet high in protein, as is evident by a comparison of the results in the various groups (table 2). As a matter of fact, in rats 23, 24, 26, 27 and 28 in group 2 (on diet 550 throughout, a diet high in protein), the lesions usually appeared less numerous and severe than in most of the rats maintained throughout on diet 550 B, which was low in protein (all of group 3, rats 47 to 51 of group 4, rats 58 to 86 of group 5 and rats 91 to 95 of group 6). On the whole, it appears improbable that the level of the dietary protein (ranging from 12 to 24 per cent) in these experiments had any appreciable effect on the incidence of the renal lesions observed.

SUMMARY

Characteristic renal lesions have been demonstrated in rats reared on Burr's highly purified diets, which are practically fat-free, but otherwise adequate.

The most striking and characteristic renal lesion is the calcification in the cells of some renal tubules and in necrotic areas of the renal medulla. In extreme cases there is complete disintegration of the apical region of the pyramid.

Various forms of renal epithelial degeneration and fatty or lipoidal changes also occur to a variable extent. These may or may not be associated with the calcification.

In the medulla, large quantities of fatty or albuminous material may accumulate, forming casts in the lumina of the tubules and especially in the papillary ducts.

An atypical (uncornified) hyperplasia is often found in the renal pelvic epithelium. This usually appears most pronounced where necrosis of the papilla is also present.

Slight focal infiltration by round cells is found in the test rats, but no more frequently than in the normal controls.

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19. Wolbach, S. B., and Howe, P. R.: The Epithelial Tissues in Experimental Xerophthalmia, Proc. Soc. Exper. Biol. & Med. **22**:402, 1925; Vitamin A Deficiency in the Guinea-Pig, Arch. Path. **5**:239, 1928.

20. Tyson, M. D., and Smith, A. H.: Tissue Changes Associated with Vitamin A Deficiency in the Rat, Am. J. Path. **5**:57, 1929.

The inclusion bodies incidentally noted in the cortical epithelium of some of the controls apparently have no relation to the disorder caused by a deficiency of fat in the diet.

The addition of from 2 to 20 per cent of lard, or of slight amounts of cod liver oil, to the diet usually prevents or cures the renal disorder, at least to a large extent. Especially the calcareous degeneration and casts are almost completely eliminated. Various other types of fat (such as corn oil, olive oil and methyl linolate) usually appear somewhat less beneficial to the kidney, in which some of the lesions persist, although the general condition of the body is cured or greatly improved.

The concentration of dietary protein, within the range used, shows no definite relation to the incidence or to the severity of the renal lesions observed.

IODINE DEFICIENCY AND GOITER

INFLUENCE OF A DIET POOR IN IODINE ON THE THYROID GLAND IN WHITE RATS *

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Chatin's [1] theory that endemic goiter is the result of a deficiency of iodine is accepted by most American scientists. In mapping the areas of the United States in which goiter is prevalent, McClendon and Hathaway [2] determined the iodine content of foodstuffs and water from goitrous and nongoitrous areas, and showed that there is little iodine in the vegetables and the waters of those parts of the United States in which simple goiter is a serious problem.

Marine and Lenhart,[3] who studied extensively the effect of iodine on the mammalian thyroid gland, arrived at the conclusion that this gland undergoes hyperplasia whenever its iodine content falls below 0.1 per cent, and that the therapeutic effects of iodine are the result of restoring to the thyroid gland the normal amount of iodine.

A direct experimental proof for the theory of Chatin has never been attempted in this country. In southern Germany, Tanabe [4] succeeded in producing hyperplasia of the thyroid gland by giving white rats a diet poor in iodine. Freiburg being situated, however, in a district where goiter is endemic, Tanabe's positive results must be regarded with great caution, since it is well known that in goitrous areas, domesticated animals incur hyperplasia of the thyroid gland spontaneously. Tanabe's successful experiments have to be repeated in a goiter-free country before they can be accepted as proof for the iodine-deficiency theory.

Wichita, Kan., is free from endemic goiter. There arises the question whether or not Tanabe's experiments would turn out to be positive also in this locality.

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1. Chatin: Recherche de l'iode dans l'air, les eaux, le sol et les produits alimentaires des alpes de la France et du Piémont, Compt. rend., Paris **33**:529 and **34**:14 and 51, 1851-1853.

2. McClendon, J. F., and Hathaway, J. C.: Inverse Relation Between Iodin in Food and Drink and Goiter, Simple and Exophthalmic, J. A. M. A. **82**:1668, 1924.

3. Marine, D., and Lenhart, C. H.: Relation of Iodin to the Structure of Human Thyroids, Arch. Int. Med. **4**:440, 1909.

4. Tanabe: Experimenteller Beitrag zur Aetiologie des Kropfes, Beitr. z. path. Anat. u. z. allg. Path. **73**:415, 1925.

EXPERIMENTS

The first series of experiments was begun in April, 1929, with two litters of young white rats, one being 12, the other 20, weeks old. The experimental lot consisted of five animals, three taken from the younger and two from the older litter. These white rats received food poor in iodine as outlined by Tanabe [4]: each was given daily from 8 to 10 Gm. of barley and distilled water, and every third day from 2 to 3 Gm. of uncooked meat and 2 Gm. of fresh lettuce. The remaining five animals from the same litters were kept as controls and were fed on a properly balanced diet and fresh city water.

The cages were kept scrupulously clean, to avoid any possible influence of filth and fecal material on the thyroid gland as pointed out by Sasaki [5] and McCarrison.[6] The floors of the cages were made of mesh wire, and no hay or other material was used for bedding.

The feeding was continued for a period of 119 days, and both lots of rats were killed with chloroform. The thyroid glands were dissected immediately after death, measured and preserved in a diluted solution of formaldehyde (1 : 10). Postmortem changes were thus prevented. No constitutional differences were noticed between the two experimental lots. The macroscopic and microscopic observations in the thyroid glands are given in tables 1 and 2.

I was unable to find any striking differences between the two groups of white rats. In the experiments described, a diet poor in iodine failed to produce the changes which Tanabe was able to see. The average body weight of the controls being 170 Gm., their thyroid lobes measured, on the average, left, 5.3 by 3.1 by 2.2 mm.; right, 5 by 3.4 by 2.6 mm. After a diet poor in iodine, the average body weight was 132 Gm. and the average size of the thyroid lobes was as follows: left, 5.4 by 3.4 by 1.9 mm.; right, 4.5 by 3 by 1.8 mm. Both groups therefore presented the same normal size that Wegelin described in white rats from goiter-free regions of Germany.

Early goiter in animals manifests itself in the small size of the acini, decrease of the colloid and columnar size of the epithelium, with formation of papilli and mitotic figures, and in hyperemia of the gland. Not one of these typical changes occurred in our animals after a diet poor in iodine. Their glands showed even a slightly more viscous colloid and lower epithelial cells than those of the controls (fig. 1).

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5. Sasaki: Zur experimentellen Erzeugung der Struma, Deutsche Ztschr. f. Chir., 1912, vol. 119; cited from Wegelin in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 545.

6. McCarrison: The Thyroid Gland in Health and Disease, London, William Wood & Company, 1917; Report on the Etiology and Epidemiology of Endemic Goiter, Compt. rend. Conférence internat. du goitre, Berne, 1927.

TABLE 1.—*Controls Receiving Well Balanced Diet*

White Rat	Sex	Weight, Gm.	Size of Thyroid Gland, Mm.	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Trachea
1	M	152	L: 4×2×1 R: 5×3×2	Most medium-sized, slightly larger in periphery; 15 acini appear without lumen	Well stained, filling one half to three fourths of each lumen; few acini contain unstained colloid	Cuboid in center, slightly smaller in periphery; occasionally plication of wall in peripheral acini	Very scanty	Many well filled capillaries	Empty	None	Leukocytic infiltration of mucosa
2	F	137	L: 5.5×3×2.5 R: 5.1×4×3	Small in center, with 35 to 40 solid; medium-sized in periphery; very few larger	Thin colloid, filling half of each lumen; few empty acini	Cuboid in most of the acini; few pyknotic nuclei; few desquamated cells	Very scanty	Capillaries well filled	Empty	Occasionally few single cells	Epithelium well preserved
3	M	152	L: 6×4×2.5 R: 5×3.9×2	Medium-sized in center, slightly larger in periphery; 15 to 20 appear solid	Thin colloid, filling third to half of each lumen	Cuboid; no degenerative changes; no desquamation	Very scanty	Capillaries poorly filled	Empty	Few cells	One side of epithelium exfoliated
4	F	219	L: 6×4×2 R: 5×4×3	Medium-sized in center, larger in periphery; about 18 without lumen	Well stained colloid, filling three fourths of each lumen; few acini empty	Cuboid in center, slightly lower in periphery; occasionally papillae in the larger peripheral acini	Very scanty	Capillaries well filled	Empty	In about 20 acini a few cells	Leukocytic infiltration of mucosa
5	M	190	L: 5×3×3 R: 5×2×3	Small and medium-sized in center; few large ones in periphery; 8 to 10 of each lobe, without lumen	Thin colloid with large vacuoli, filling third to half of each lumen; very few acini completely filled	Cuboid in center and in periphery; no papillae; no mitotic figures	Very scanty	Well filled capillaries	In few lymph spaces, colloid-like material	None	Normal, well preserved mucosa

TABLE 2.—*Experimental Series 2, Fed Barley and Distilled Water, with Every Third Day 2 Gm. of Lettuce and Meat, for 119 Days*

White Rat	Sex	Weight, Gm.	Size of Thyroid Gland, Mm.	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Trachea
1	F	181	L: 6×4×2 R: 5×3×2	Medium-sized in center, very large in periphery; 3 to 4 acini solid	Densely stained, filling lumen three fourths or completely; no empty acini	Flat, cuboid in center; flatter in periphery; no mitotic figures, no degenerative changes of the nuclei	Very scanty	Capillaries moderately filled	Colloid-like material in few	None	Well preserved, normal mucosa
2	M	143	L: 5×3×1.5 R: 5×3×1.5	Medium-sized in center, many larger in periphery; none solid	Densely stained, filling most of the acini completely; no empty acini	Flat, cuboid; no mitotic figures, no degenerative changes	Very scanty	Some capillaries well filled	Colloid-like material in few	None	Exfoliation of epithelium
3	M	134	L: 5×3×2 R: 6×4×2	Small and medium-sized in center, none large; 15 to 18 solid	Densely stained, filling most of acini completely; no vacuoli	Flat, cuboid; no papillae; no mitotic figures	Very scanty	Capillaries poorly filled	Colloid-like material in few	None	Epithelium well preserved
4	F	123	L: 6×4×2 R: 6×3×2	Small and medium-sized in center, larger in periphery; about 17 solid	Not thick, filling lumen three fourths or completely; occasionally empty acini	Cuboid in center, lower in periphery; few papillae	Very scanty	Capillaries very well filled	Colloid-like material in very few	None	Part of epithelium exfoliated
5	M	79	L: 5×3×2 R: 5×2×1.5	Medium-sized in center, small in isthmus, many large in periphery; 15 without lumen	Well stained colloid, filling three fourths of each lumen; no empty acini	Mostly cuboid, slightly lower in periphery; no papillae; no mitotic figures	Distinct fibrous septums	Capillaries not filled; larger vessels contain much blood	Empty	None	Leukocytic infiltration of mucosa

After this unsuccessful attempt to confirm Tanabe's results, the experimental conditions were made more severe. Lettuce was excluded from the food completely, since green leaves constitute the most important source of iodine intake. This second experiment was carried out on five young white rats, their food consisting exclusively of barley and distilled water. This feeding was continued with the same individuals

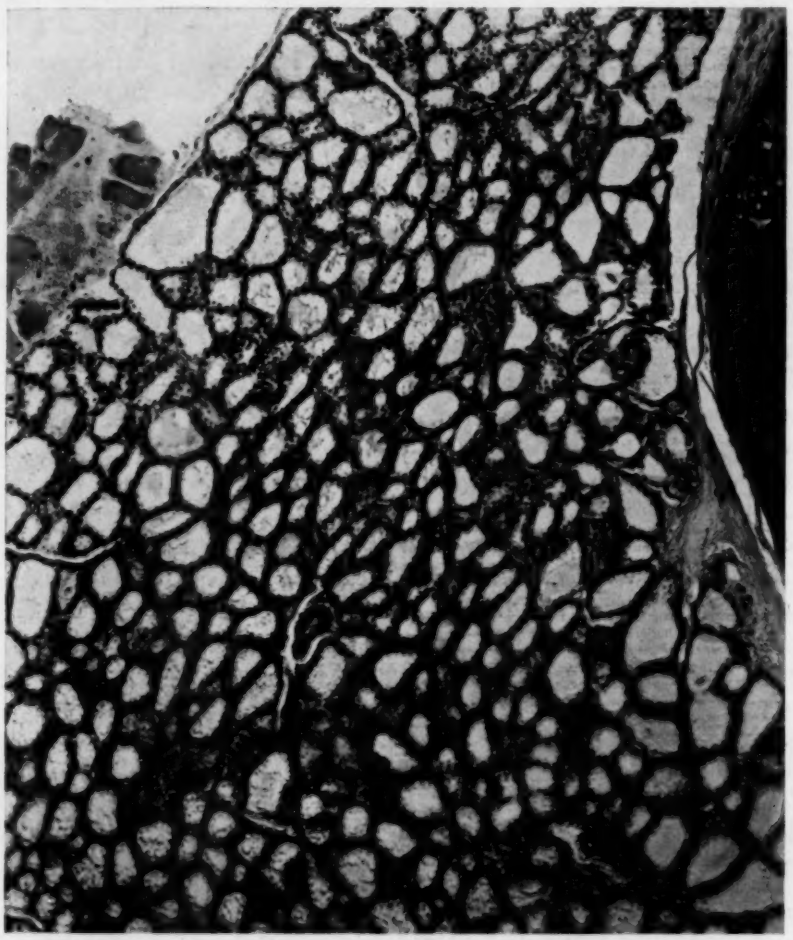

Fig. 1.—Normal thyroid gland of the white rat (control series 1).

for a period of 90 days. But even this strict iodine-free diet failed to cause any enlargement of the thyroid gland. On the contrary, all the animals of this series showed definitely smaller glands than the controls, not only absolutely, but also relative to their body weight. The five animals, after being chloroformed to death, weighed, on the average, 152 Gm.; the average size of the left lobe was 4.4 by 1.9 by 2.2 mm.; of the right, 4.6 by 2.2 by 2.4 mm. Microscopically, these glands

presented signs of atrophy, the follicles being small and filled with intensely stained colloid; the epithelium was low, and the capillaries were poorly filled with blood (table 3 and fig. 2). Thereafter, a prolonged attempt was made with the same diet on four other rats, and the feeding was continued over a period of 160 days. In all these four animals identical changes occurred, namely, a still more pronounced atrophy of the thyroid gland. The average body weight of these four animals was 125 Gm.; the average size of the left lobe was 4.7 by 2 by 1.8 mm., that of the right, 4.7 by 2.2 by 1.8 mm. The microscopic examination revealed small acini with very viscous colloid, a low epithelial cell layer and poor filling of the capillaries with blood (table 4).

The completely negative results of my three experiments, which were instituted under even stricter conditions than those of Tanabe, are surely not in favor of the generally accepted theory that hyperplasias of the thyroid gland, including endemic goiter, are due to insufficiency of iodine in the diet of the individuals. My observations, on the contrary, make it clear that a diet poor in iodine produces atrophy of the thyroid gland, the severity of which is in inverse proportion to the amount of iodine taken and in direct proportion to the length of time the feeding experiments are continued. My results confirm the view held by Wegelin, that endemic goiter cannot be explained as compensatory hypertrophy of the thyroid gland, due to a low content of iodine in the food, but rather that, in insufficiency of iodine, atrophy of the organ must be expected, since iodine is a strong stimulant to the action of the thyroid gland.

Without questioning the important rôle that sufficiency of iodine may play in the prevention of goiter, I am led to the belief that the essential cause of goiter is a positive agent. As one of the possible positive factors, a high content of calcium in the drinking water is held responsible by several investigators for the development of goiter. McClelland,[7] Bouchardat,[8] Billiet,[9] Boussingault[10] and Pighoni[11] advanced the theory that an excess of calcium sulphate or carbonate

7. McClelland: On the Connection Between Goiter and Cretinism, Their Nature and Causes in: Some Inquiries in the Province of Kemaon Relative to Geology and Other Branches of Natural Science, Including an Inquiry into the Causes of Goiter, Calcutta, 1835; Dublin J. Sc. **11**:295, 1837.

8. Bouchardat: De l'influence de la qualité des eaux sur la production du goitre et du crétinisme, Bull. de l'Acad. nat. de méd., 1851; cited from Wegelin (footnote 5, p. 537).

9. Billiet: Observations sur le récensement des personnes atteintes de crétinisme, Ann. d'hyg., 1853, vol. 50; cited from Wegelin (footnote 5, p. 538).

10. Boussingault: Mémoires sur les salines iodiféres des Andes, Ann. de chim. et de phys., vol. 54; cited from Wegelin (footnote 5, p. 538).

11. Pighoni: Ricerche sulla endemia gozzo-cretinica nella regioni veneto-lombarde e nella provincia di Reggio-Emilia, Riv. sper. di freniat. **44**:66, 1920.

TABLE 3.—*Experimental Series 3, Fed Barley and Distilled Water for Ninety Days*

White Rat	Sex	Weight, Gm.	Size of Thyroid Gland, Mm.	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Trachea
1	M	80	L: 4×2×1.5 R: 4×2×1.5	Most small-sized, in periphery several medium-sized; 4 or 5 solid	Densely stained, filling lumen three fourths or completely	Cuboid and low cuboid; no papillae; no mitotic figures	Very scanty	Capillaries very poorly filled, larger vessels well filled	Filled with colloid-like material	In few acini	Very well preserved mucosa
2	F	135	L: 4.5×2×3 R: 5×2×2	Small and medium-sized in center, slightly larger in periphery; 4 or 5 solid	Well stained, filling of each lumen three fourths	Low cuboid; no papillae; no degenerative changes; no mitotic figures	Very scanty	Capillaries not filled, larger vessels moderately filled	Well filled with colloid-like material	None	Well preserved mucosa
3	M	220	L: 4×2×2 R: 4×2×3	Small in center, medium-sized in periphery; 6 to 8 solid	Well stained, filling lumen three fourths or wholly	Cuboid and low cuboid; no proliferative changes	Very scanty	Capillaries not filled, larger vessels well filled	Well filled	None	Well preserved mucosa
4	M	135	L: 5×2×2 R: 5×1.5×2.5	Small in center, occasionally medium-sized in periphery	Well stained, filling acini only about one fourth full	Cuboid and low cuboid; no papillae	Very scanty	Capillaries not filled, larger vessels well filled	Well filled	None	Well preserved epithelium; marked lymphocytic infiltration
5	F	117	L: 4×1.5×2 R: 4.5×1.5×2	Small and medium-sized, very few larger	Thin and moderately viscous, filling more than half of each lumen	Low cuboid; no proliferation; no mitotic figures	Very scanty	Capillaries not filled, larger vessels moderately filled	Few contain colloid-like material	None	Well preserved epithelium; marked lymphocytic infiltration

TABLE 4.—*Experimental Series 4, Fed Barley and Distilled Water for 160 Days*

White Rat	Sex	Weight, Gm.	Size of Thyroid Gland, Mm.	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Trachea
1	M	80	L: 4×2×2 R: 4×1.5×2	Small in center, medium-sized in periphery; 4 to 5 solid	Most of acini empty; thin colloid in few peripheral ones	Cuboid; nucleus pyknotic in many cells	Very scanty	Very strongly filled capillaries	Empty	Extensive	Epithelium not well preserved
2	F	119	L: 4.5×2×1.5 R: 4.5×2×2	Small; in periphery, few larger; 8 solid	Very dense, completely filling most of the acini	Low cuboid; no papillae; no mitotic figures	Very scanty	Capillaries well filled	Empty	None	Well preserved epithelium
3	F	134	L: 5×2.5×3 R: 4.5×2×2	Small; in periphery, some medium-sized; 10 solid	Thin colloid filling most of acini; in peripheral acini, only part of each lumen filled	Cuboid; no papillae; no mitotic figures	Very scanty	Capillaries well filled	Empty	None	Well preserved epithelium
4	M	132	L: 4.5×2×1 R: 5×2×1.5	Most small; 3 or 4 solid	Densely stained, filling most of acini	Cuboid and low cuboid; no papillae	Very scanty	Very well filled capillaries	Empty	None	Well preserved epithelium

may cause endemic goiter. In a recent paper, Kottmann [12] pointed out that calcium decreases the dispersity of the blood serum and increases the viscosity of the thyroid colloid. Abelin [13] was able to demonstrate in experiments on white rats that an excess of calcium lowers the

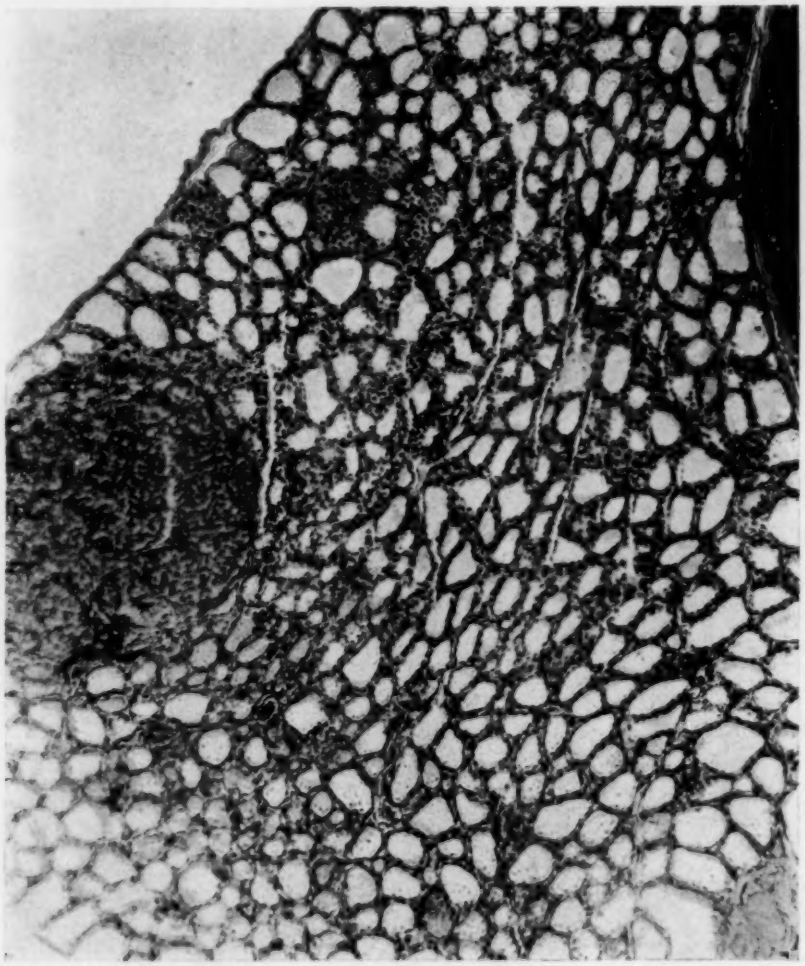

Fig. 2.—Thyroid gland after iodine-free diet for ninety days (experimental series 3).

12. Kottmann: Kolloidchemische Untersuchungen über Schilddrüsenprobleme, Schweiz. med. Wchnschr. **50**:644, 1920.

13. Abelin, I.: Schilddruese und Mineralstoffwechsel. Einfluss des Dinatriumphosphats und der Kalziumsalze auf die Wirkung der Schilddruesensubstanzen, Biochem. Ztschr. **72**:199, 1928.

metabolic action of thyroxine. Wilms[14] and Répin[15] observed that water from goitrous districts will lose its activity after precipitation of its calcium by boiling. Geologic studies are also in favor of this theory. McCarrison,[6] in his analysis of conditions in the goitrous regions of Chivral and Gilghit in northern India, found that there are certain large

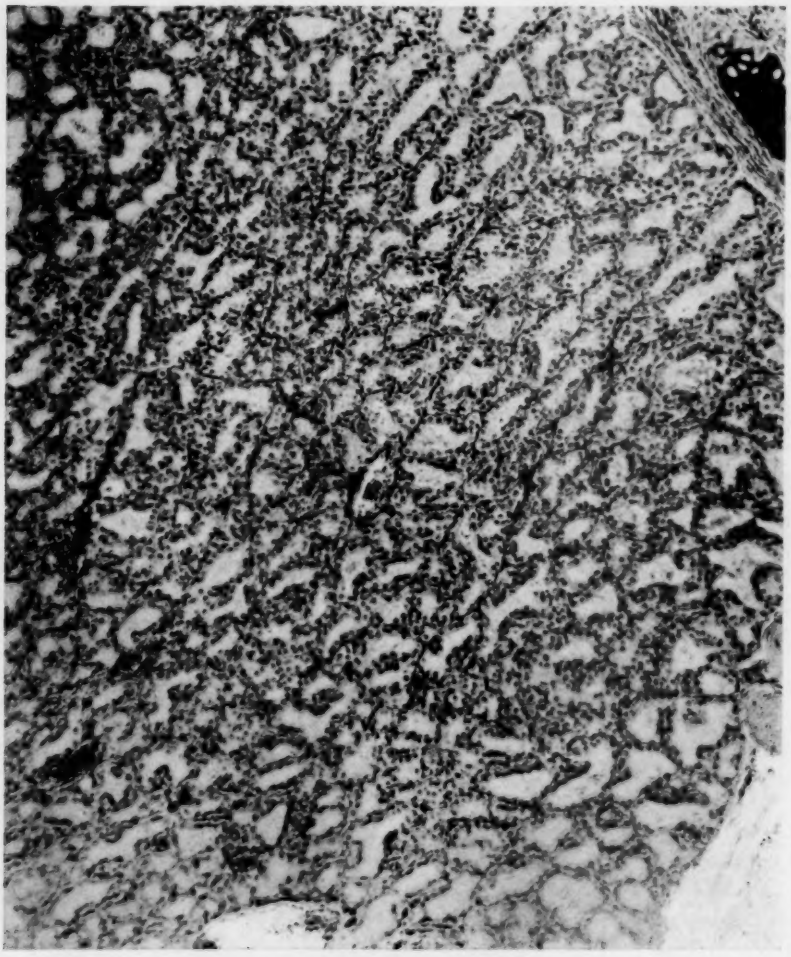

Fig. 3.—Hyperplastic goiter after diet rich in calcium and free from iodine for eighty-five days (experimental series 5).

outcrops of limestone, and that it is from these that the villages in which goiter is most prevalent derive their supply of water.

14. Wilms: Ursache und experimentelle Erzeugung des Kropfes, Zentralbl. f. Chir., 1910, vol. 37, no. 31; Ursache und experimentelle Erzeugung des Kropfes, Deutsche med. Wchnschr. **36**:604, 1910.

15. Répin: Les eaux goitrigenes, Rev. d'hyg. **33**:317, 1911.

Also from Tanabe's recent experiments in the Institut of Aschoff it appears that diets high in calcium and, at the same time, low in iodine produce the most pronounced hyperplasias of the thyroid gland.

I studied the influence of drinking water rich in calcium on eight young rats. They were fed only barley and as drinking water a pure

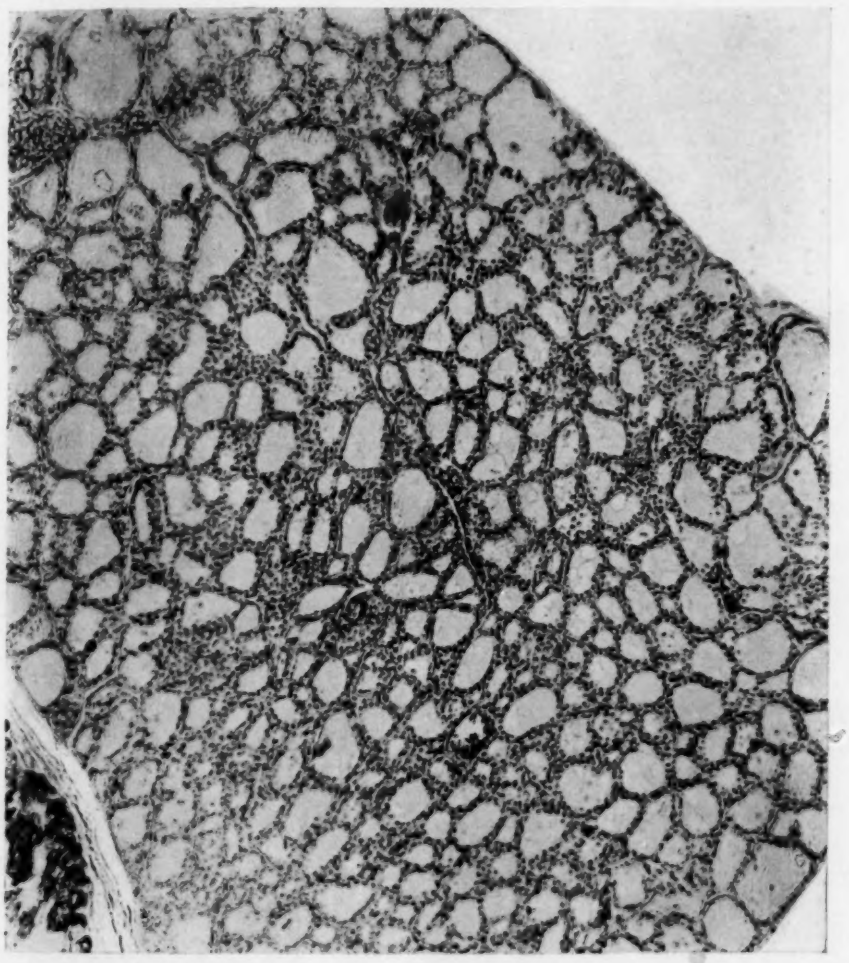

Fig. 4.—Small colloid goiter after a diet rich in calcium and iodine for seventy days (experimental series 6).

2 per cent solution of calcium chloride. After a period of ninety days, five of these animals were killed with chloroform and their thyroid glands examined. The observations were uniform in all. The thyroid glands were distinctly enlarged and appeared very hyperemic. The average weight of this series being 158 Gm., the average size of the thyroid lobes was as follows: right, 5.6 by 2.3 by 3.5 mm.; left, 6 by

TABLE 5.—*Experimental Series 5, Fed Barley and Calcium-Rich Water for Eighty-Five Days*

White Rat	Sex	Weight, Gm.	Size of Thyroid Gland, Mm.	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Trachea
1	M	110	L: 6×3×2 R: 6×3×2	Narrow tubules, with papillations; very many solid	Most of acini empty; in few, central small globule of dark colloid	High columnar with plications and papillae; occasionally, mitotic figures	Very scanty	Capillaries much dilated and well filled	Empty	None	Well preserved epithelium; round cells in submucosa
2	F	182	L: 6×3×4 R: 6×4×4	Elongated, narrow tubules with papillations; few solid	Most of acini empty; granular colloid in few	Columnar, with papillae; no mitotic figures; few large, dark nuclei	Very scanty	Hyperemic	Empty	None	Well preserved epithelium
3	F	122	L: 6×3×2.5 R: 5.5×2×3.5	Smallest and small	Most of acini appear empty; granular colloid in few	High cuboid; no papillae	Very scanty	Hyperemic	Empty	None	Well preserved epithelium
4	F	140	L: 6×2.5×3 R: 5.5×2×3.5	Narrow tubules, irregular in form; 6 to 8 solid	Most of acini empty; very thin colloid in few	High cuboid; in several acini, papillae; occasionally, very large nuclei; no mitotic figures	Very scanty	Hyperemic	Empty	None	Well preserved epithelium
5	M	138	L: 6×2×3 R: 5.5×2×3	Narrow tubules of irregular form; 3 to 4 solid	Acini empty	Columnar epithelium with papillae in peripheral acini	Very scanty	Well filled	Containing some colloid-like material	None	Well preserved epithelium

TABLE 6.—*Experimental Series 6, Fed Calcium-Rich Water, with Well Balanced Diet for Seventy Days*

White Rat	Sex	Weight, Gm.	Size of Thyroid Gland, Mm.	Acini	Colloid	Epithelium	Fibrous Tissue	Blood Vessels	Lymph Spaces	Desquamation	Trachea
1	F	90	L: 4×1.5×2 R: 5.5×2×2	Large in periphery, medium-sized and small in center; none solid	Well stained, filling most of acini completely	Low cuboid; no papillae	Very scanty	Moderately filled	Several filled with blood	Extensive	Leukocytic infiltration
2	F	170	L: 7×2×2 R: 6.5×3×1.5	Middle-sized in center, larger in periphery; none solid	Densely stained, filling most of acini completely	Cuboid; in few peripheral acini, papillae	Very scanty	Capillaries moderately filled, larger vessels well filled	Empty	None	Well preserved; no inflammation
3	F	120	L: 6×3×1.5 R: 6×3×1.5	Middle-sized and small in center, few larger in periphery	Very thin or unstained in many acini, well stained in peripheral acini	Cuboid; no mitotic figures; no papillae	Very scanty	Extensively hyperemic	Not filled	None	Well preserved

2.9 by 2.9 mm. In their microscopic picture all five thyroid glands presented a marked epithelial hyperplasia. The acini formed elongated narrow tubules with high columnar cells; the walls formed infoldings and plications; the colloid did not stain at all or very faintly, and many acini appeared solid. The blood vessels were much dilated; the capillaries between the acini contained a great amount of blood. Thus the histologic changes corresponded completely to the description which Langhans and Wegelin,[16] and Marine and Lenhart [3] gave of the mammalian hyperplastic goiter (table 5 and fig. 3).

Three of the eight animals were kept alive for another period of seventy days, the water rich in calcium being given to them but the diet poor in iodine being replaced by a well balanced one, with plenty of green vegetables. After 70 days, these animals still showed a definite enlargement of the thyroid glands, but without hyperemia. The average body weight in this series was 145 Gm.; the average size of the thyroid glands was: right, 6.3 by 3 by 1.5 mm.; left, 6.5 my 2.2 by 1.8 mm. Histologic examination revealed large acini with cuboid epithelium; the colloid stained densely; the blood vessels were only moderately filled with blood. Several lymph spaces between the acini contained material that stained like colloid. These glands represented, therefore, small goiters of the colloid type (table 6 and fig. 4).

The last experimental results conform to the work of McCarrison,[6] who produced small colloid goiters by a diet rich in calcium, but otherwise well balanced.

That an excess of iodine in the drinking water exerts an inhibitory action on hyperplasia of the thyroid gland—in spite of a high content of calcium—was demonstrated clearly by Tanabe.[4]

COMMENT

In table 7, the average size of the thyroid glands and the average body weight of each experimental series are tabulated. From the negative results of my attempt to produce goiter by means of an insufficiency of iodine in the food inferences may be drawn that lack of iodine is neither the only nor the essential cause of endemic goiter. The positive results of the second experimental series with a diet rich in calcium indicate that a positive agent is responsible for the development of goiter. This positive agent may not be a single specific factor, and this or these positive agents may not alone cause hypertrophy of the thyroid gland in the presence of a high amount of iodine in the food, nor may insufficiency of iodine in itself cause endemic goiter in the absence of the other agents that cause goiter, but when both are present, the conditions for the development of hyperplastic goiter seem to be at their optimum. Only by this conception of the etiology of goiter

16. Langhans and Wegelin: Der Kropf der weissen Ratte, Bern, Paul Haupt, 1919.

is one able to understand why endemic goiter may be present in localities rich in iodine, and, on the other hand, absent in regions poor in iodine.

The last experimental series in which hyperplastic goiter was produced with a diet rich in calcium and poor in iodine and colloid goiter with a diet rich in calcium and iodine are not in favor of McCarrison's theory that these two types of goiter are entirely different from the etiologic standpoint, but indicate that the different structure of the thyroid gland depends on the amount of iodine in the food, the essential cause of the enlargement in each case being identical.

Comparative studies, made in Europe following a suggestion of Aschoff, have shown that the histologic structure of goiters varies according to the part of the country in which they occur. In certain regions, especially in level regions, the diffuse colloid goiter, with and without hyperthyroidism, and exophthalmic goiter predominate. In

TABLE 7.—*Average Weight of Animals and Average Size of Thyroid Glands in All Six Experimental Series*

Series	Diet	Duration, Days	Weight, Gm.	Right Lobe, Mm.	Left Lobe, Mm.
1	Mixed diet	119	170	5×3.4×2.6	5.4×3.1×2.2
2	Barley, distilled water, every few days lettuce, meat	119	132	5.4×3 ×1.8	5.4×3.4×1.9
3	Barley and distilled water	90	152	4.5×2.6×2.3	4.4×1.9×2.2
4	Barley and distilled water	160	125	4.7×2 ×1.8	4.7×2.2×1.8
5	Barley and 2% calcium chloride	85	158	5.6×2.3×3.5	6 ×2.9×2.9
6	Mixed diet and 2% calcium chloride	70	145	6.3×3 ×1.5	6.5×2.2×1.8

more mountainous countries the toxic goiter is an exception, and the nearer one approaches the center of the endemic area the less one meets with the colloid goiter. It is replaced by the colloid-poor, diffuse parenchymatous goiter in childhood and by the adenomatous parenchymatous nodular goiter with its degenerative forms in adults. It can hardly be doubted that, as in my last experimental series, these differences in the architecture of the goiters are due to differences in the iodine content of the food, the positive etiologic factor, hitherto unknown, being the same and being world-wide.

SUMMARY

Attempts to produce goiter in white rats by feeding a diet poor in iodine gave only negative results.

Excess of calcium in the drinking water and a low intake of iodine caused a marked epithelial hyperplasia of the thyroid gland.

Drinking water rich in calcium and a diet rich in iodine produced small colloid goiters.

Insufficiency of iodine was shown not to be the essential cause of goiter.

THE EFFECT OF EXPOSURE TO AN ULTRAHIGH FREQUENCY FIELD ON GROWTH AND ON REPRODUCTION IN THE WHITE RAT*

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Since the development of a high frequency oscillator for the production of artificial fever in man,[1] it has become of increasing importance to know the biologic reactions produced by such an agent. Christie and Loomis,[2] and Kahler, Chalkley and Voegtlin [3] expressed the belief that the effect of a high frequency field depends primarily on the production of a rise in temperature in the organism, while Schereschewsky [4] stated that certain wave lengths (from 15 to 3.8 meters) exert a specific effect on living cells. An investigation was accordingly planned to determine the effect of exposure to a high frequency field on growth and reproduction in the white rat.

The high frequency oscillator used in these experiments was constructed on the same principle as a short wave radio transmitter, with the exception that the energy is concentrated between two condenser plates instead of being directed from an aerial. The heater was designed by the General Electric Company [5] and consists of a vacuum tube oscillator and rectifier that supplies the high voltage for the oscillator. The high frequency oscillator is composed of two 75 watt radiotrons operating at a frequency of from 9,000 to 12,000 kilocycles. An air-cooled transformer having a 4,500 volt secondary and feeding a full wave rectifier forms the 2,000 volt direct current plate supply for the oscillator.

Young white rats weaned at 28 days of age and weighing from 40 to 55 Gm. were used in these experiments. There were two different series of experiments, one of which was carried out in the early part of 1929 and the other in the early part of 1930.

* Submitted for publication, Oct. 27, 1930.

* From the Department of Biochemistry, Union University Medical Department, Albany Medical College.

1. Carpenter, C. M., and Page, A. B.: Science **71**:450, 1930.

2. Christie, R. V., and Loomis, A. L.: J. Exper. Med. **49**:303, 1929.

3. Kahler, H.; Chalkley, H. W., and Voegtlin, C.: Pub. Health Rep. **44**:339, 1929.

4. Schereschewsky, J. W.: Pub. Health Rep. **41**:1939, 1926.

5. Dr. W. R. Whitney of the General Electric Company placed the apparatus at our disposal and members of his research staff, particularly A. B. Page and K. C. DeWalt, gave technical assistance from time to time.

In the first series of experiments there were six male and eight female rats. These rats were put on the Sherman diet B,[6] which was used at that time as our stock ration diet. The rats were divided into two groups so that litter mates were evenly distributed in each group, and one of the groups was exposed to a high frequency field while the other was kept as control. The high frequency exposure was given five days a week over a period of from sixty to ninety days. The length of each treatment for the first two weeks was thirty minutes, and then it was increased to forty-five minutes. The rats were heated each day to a rectal temperature of from 39.4 to 40.5 C. and kept in that range for from fifteen

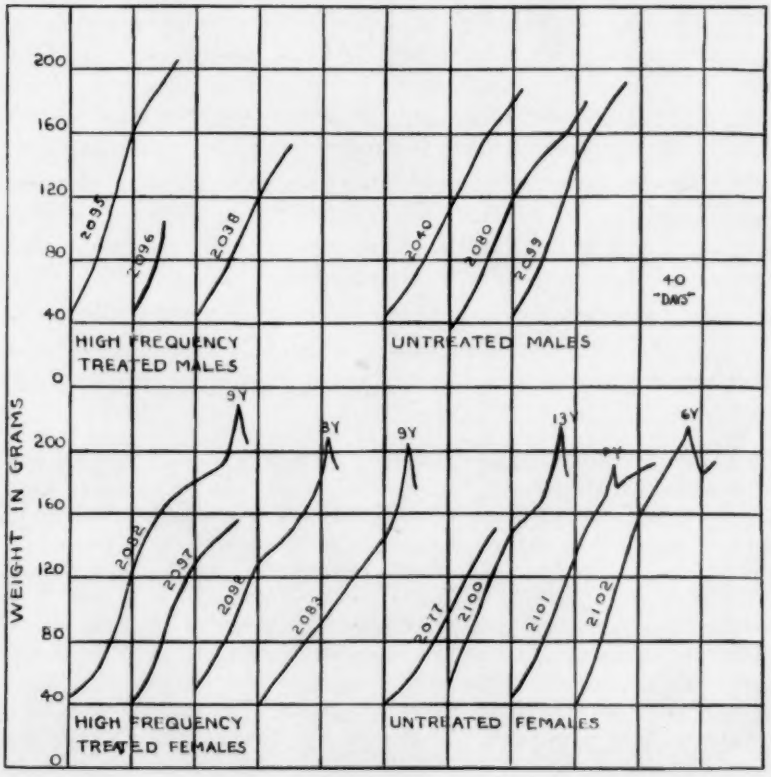

Chart 1.—Experiments of the 1929 series showing the effect on growth of exposure of rats to ultrahigh frequency field. Rats in this series were fed on Sherman's diet B.

to thirty minutes. The normal rectal temperature of the rats varied from 37 to 37.5 C. Our plan was to heat the rats to the required temperature in from fifteen to twenty minutes, and then maintain them at that temperature. It was difficult to keep the rats at any set temperature, and it was necessary to record the rectal temperatures at intervals of from fifteen to twenty minutes in order to adjust the distance of the plates to keep the rats from getting either too warm

6. Sherman, H. C., and Muhlfeld, M.: J. Biol. Chem. **53**:41, 1922.

or too cool. The results of this group of experiments on growth are plotted in chart 1. A summary of the young born and reared by the heated and unheated mother rats in both series of experiments is given in the table.

In the second, or 1930, series of experiments, there were fourteen rats. The seven males were litter mates, four of which were given high frequency treatment and three kept as controls. The seven females were also litter mates, four being given treatment and three kept as controls. These rats were all put on Bills' modification[7] of Steenbock's stock diet, which we adopted in this laboratory in the summer of 1929, and have found very satisfactory. The second series of rats were also treated five days a week over a period of from ninety to one hundred

Effect of Repeated Exposure to High Frequency Field on Reproduction and Rearing of Young

Experiment Series	Rat Number	High Frequency Exposure	Age at Birth of First Litter, Days	Number in Litter	Number Weaned at 28 Days of Age	Average Weight of Young at Weaing, Gm.	Comment
1929	2082	Treated	132	9	6	43	
	2097	Treated	...	..	...	..	No litter during period of observation
	2098	Treated	114	8	8	42	
	2083	Treated	122	9	6	45	
1929	2077	Untreated	...	..	...	..	No litter during period of observation
	2100	Untreated	96	13	9	45	
	2101	Untreated	92	?	2	47	
	2102	Untreated	98	6	4	46	
1930	2385	Treated	146	13	8	47	
	2386	Treated	146	8	0	..	Rat developed infection and young died at 4 days of age
	2387	Treated	...	..	...	..	Died after sixth treatment from too high temperature
	2388	Treated	155	8	6	44	
1930	2389	Untreated	117	11	8	44	
	2390	Untreated	116	10	7	50	
	2391	Untreated	123	9	6	54	

and twenty days. The length of each treatment in this series was increased to one hour, and the temperature was brought up to from 40.2 to 40.5 C. in the first half hour and then maintained at that temperature for the next half hour. Occasionally, the temperature rose to 41.6 C., and in one instance five of the seven rats were heated to a temperature of from 43.3 to 43.9 C. One of the rats in this group died. The female rats in this series were not mated until they were 90 days of age. The growth curves of these rats are plotted in chart 2 and the table contains the record of young born and reared by the mother rats of this series.

We realize that the number of rats used in these two series of experiments is too few to draw any sweeping conclusions, but nevertheless they do show several interesting points. One reason for using

7. Bills, C. E.; Honeywell, E. M., and MacNair, W. A.: J. Biol. Chem. **76**:251, 1928.

so few animals is that we could not heat more than three or four at one time, and our constant attention was required during the high frequency treatment. On examination of charts 1 and 2, it will be noted that the growth curves for the two groups (treated and untreated) of rats in

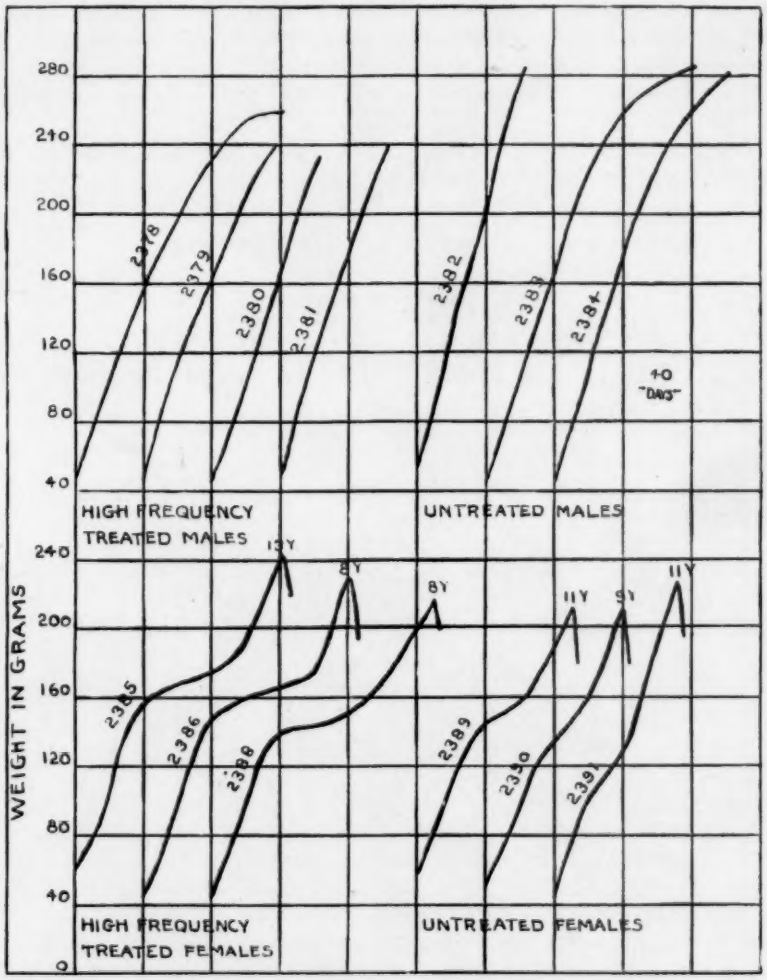

Chart 2.—Experiments of the 1930 series showing the effect on growth of exposure of rats to ultrahigh frequency field. Rats in this series were fed on Bills' modification of Steenbock's stock diet.

each series run closely parallel. We might say that the heated rats are just a trifle stunted in their growth, although the number of rats studied are too few to draw this conclusion. In other words, rats can be heated repeatedly to from 39.5 to 40.5 C. without any marked interference in

their growth, and it should be emphasized that these experiments are at the period of greatest growth impulse. Another interesting point in regard to these two charts is that the growth curve of the 1930 series is much better than the 1929 series. The growth curve for the 1929 series follows closely that given by Donaldson.[8] The growth curve for the 1930 series is similar to that reported by Smith and Bing.[9]

The data on reproduction and rearing of the young are also of considerable interest. In the first series of experiments the males and females were not caged separately, and it will be noted from the table that the treated females did not have young until an average period of 120 days of age while the untreated females had young at 95 days of age. There is also a slight difference in the two groups, in the weight of the young at the age of weaning, but the difference is so small and the number of young averaged is not sufficient to draw any definite conclusions.

In the 1930 series, the females were not mated until they were 90 days of age; nevertheless, the treated females did not have young until an average period of thirty days later. Again, there is a slight difference in the two groups in the average weight of the young at time of weaning.

A pathologic examination of the tissues of a number of these rats that were treated for a period of three months was made by members of the Department of Pathology.[10] They reported that the treated animals showed little change from the untreated ones. In the males, there was often observed an exhaustion or marked retardation of spermatogenesis with exfoliation of the germinal epithelium and proliferation of Sertoli's cells.

CONCLUSIONS

Exposure of young rats to an ultrahigh frequency field for periods of from one-half to one hour daily and raising their body temperature to 40.5 C. does not seem to retard their growth appreciably. The reproductive organs in the male and female rats are not appreciably affected, so that there is no loss in power to breed. Repeated exposure of rats to an ultrahigh frequency field in which the body temperature is raised to 40.5 C. does not produce any abnormal pathologic lesions.

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8. Donaldson, H. H.: The Rat, ed. 2, Philadelphia, Wistar Institute, 1924, p. 176.

9. Smith, A. H., and Bing, F. C.: J. Nutrition **1**:179, 1928.

10. Dr. V. C. Jacobson and Dr. K. Hosoi examined the tissues of these rats.

PHYSIOLOGIC AND BIOCHEMICAL CHANGES RESULTING FROM EXPOSURE TO AN ULTRAHIGH FREQUENCY FIELD*

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The study of the biologic effects on animals of electrical oscillations of very high frequency generated by a vacuum tube oscillator has opened a new field of investigation. During the operation of a short wave radio transmitter, striking heating effects in the vicinity of the antenna were noted.[1] Hosmer has shown that there is a well defined relation between the rate of heating of solutions of different salt content and the frequency of voltage alternations. Thus at a frequency of 25,000,000 cycles (12 meters wave length), a 0.05 per cent solution of sodium chloride heats fastest, while at a frequency of 10,000,000 cycles a 0.025 per cent solution heats fastest. Solutions of different salts but of the same electrical conductivity, heat alike. The heating effect is developed within the solution itself. The plates remain cold at all times and are separated by an air gap from the introduced container and other objects under study. Contact with plates will produce arcs and burning and charring of inflammable materials which touch them.

The first scientific investigation of the effect of these oscillating fields on living cells was reported by Gosset, Gutmann, Lakhowsky and Magrou in 1924.[2] They showed that plant tumors exposed to the radiation from a vacuum tube oscillating at 150,000,000 cycles per second (2 meters wave length) were destroyed. Schereschewsky[3]

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* A preliminary report of this paper, under the title "Chemical Changes in the Body Resulting from Exposure to Ultra High Frequency Field: I. Blood Chemical Findings in the Dog; II: Acid-Base Balance in the Plasma of Dogs," was given at the Thirteenth International Physiological Congress, held at Boston, August, 1929.

1. Hosmer, H. R.: Science **68**:325, 1928.

2. Gosset, A.; Gutmann, A.; Lakhowsky, G., and Magrou, J.: Compt. rend. Soc. biol. **91**:626, 1924.

3. Schereschewsky, J. W.: Pub. Health Rep. **41**:1939, 1926.

studied the effect of these radiations on mice. With frequencies varying from 8,300,000 to 135,000,000 cycles per second (equivalent of wave length from 36.1 to 2.2 meters), he observed severe symptoms which may result in death if the exposure is prolonged. Part of the symptoms, at least, he assumed is due to heat retention. He also claimed that the band of frequency between 20,000,000 and 80,000,000 cycles per second (wave lengths from 15 to 3.8 meters) exerts a specific effect on living cells. The rectal temperature of a live mouse could be raised from 5 to 6 C. by these currents, while that of a freshly killed mouse could be raised only from 0.1 to 0.7 C. in a similar length of time, which was taken to indicate that the heating effect with these currents was different from the diathermic effect observed at lower frequencies. In a subsequent paper,[4] Schereschewsky proceeded to investigate the effect of these radiations on transplantable tumors and claimed that he has been able to produce complete recession of the tumor and consequent recovery of the tumor-bearing animal.

Christie and Loomis [5] do not support the theory of Schereschewsky that certain wave lengths have a specific action on living cells. They studied the effect of frequencies ranging from 8,300,000 to 158,000,000 cycles and showed that the lethal nature of these radiations is proportionate to intensity of the field up to a frequency of about 50,000,000 cycles. At frequencies higher than this, the lethality of the radiation appears to diminish. They expressed the belief that the lethal effect of these currents is fully explained on the basis of the heat generated by high frequency currents which are induced in them. In experiments with *Paramecium*, Kahler, Chalkley and Voegtlin[6] agreed with Christie and Loomis that the effect of a high frequency field depends primarily on the production of a rise in temperature in the organism.

In view of the fact that the general effect on animals when placed in a high frequency field is a marked heat production throughout the body and that the method of heating promises to be of considerable therapeutic value, it was thought that it would be of particular interest to study some of the chemical changes produced in the body.

PHYSICAL APPARATUS

For generating the high frequency oscillatory current, an oscillator designed by the General Electric Company, delivering 150 watts of power at high frequencies of from 9,000 to 12,000 kilocycles was used. The details of the hookup are shown in figure 1, and figure 2 shows the general appearance of the apparatus

4. Schereschewsky, J. W.: Pub. Health Rep. **43**:927, 1928.

5. Christie, R. V., and Loomis, A. L.: J. Exper. Med. **49**:303, 1929.

6. Kahler, H.; Chalkley, H. W., and Voegtlin, C.: Pub. Health Rep. **44**:339, 1929.

as used in our experiments with the crate in position between the condenser plates. The condenser plates are adjustable as to height and spacing. These adjustments allow accommodation for various sizes of materials. Dr. W. R. Whitney of the General Electric Company, placed the apparatus at our disposal, and members of his research staff, particularly A. B. Page and K. C. DeWalt, gave technical assistance from time to time.

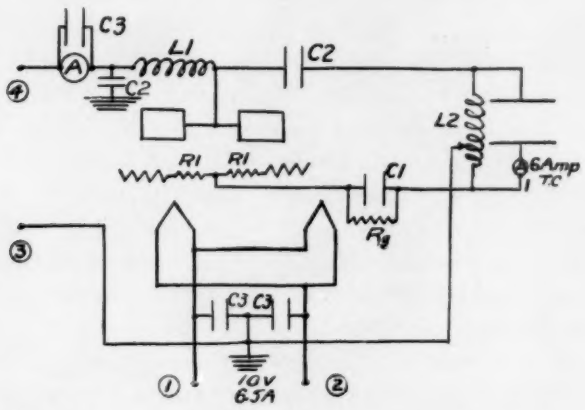

Fig. 1.—Wiring diagram of a 30 meter oscillator equipped with two UX 852 tubes. *A1* indicates 0-6 amperes full scale deflection thermocouple ammeter, type Do6; *A2*, 0-500 milliamperes full scale deflection ammeter, type Do4; *L1*, chock coil; *L2*, 8 turn coil copper wire ¼ by 5/16 inch; *C1*, 0.002 microfarad capacity condenser UC 1014 or 1874K; *C2*, condenser UC 2224; *C3*, Faradon model T condenser, 0.01 microfarad capacity; *Rg*, large blue sticks, resistance 10,000 ohms; *R1*, resistance, 10 volts, 6.5 amperes.

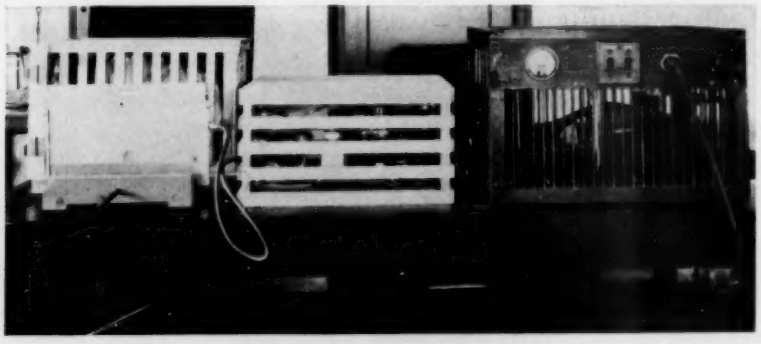

Fig. 2.—High frequency oscillator.

EXPERIMENTAL WORK

The experiments about to be described were planned to determine the chemical alterations brought about by excessively high temperatures produced by ultrahigh frequency and to determine, if possible, by

chemical methods, temperatures at which it would be safe to heat animals without producing any serious damage.

Unfortunately, no laboratory animal which could be strictly comparable to man (except perhaps the horse) seems to be entirely suitable for these experiments. Facilities for handling horses were not available, and dogs were therefore selected as being the best adapted for the work. In these experiments, the changes produced in the blood were studied because of the rapidity and accuracy with which it reflects changes taking place throughout the organism and because of the ease with which it can be sampled at intervals without producing any serious impairment per se.

All the dogs used in these experiments were mongrels varying in weight from 7 to 25 Kg. They were put on Cowgill's [7] "synthetic" food mixture. During the period of eighteen hours preceding each experiment, no food was given.

The general procedure in our experiments was to bleed the dog from the external jugular vein before and after exposure to high frequency treatment. In collecting the blood, great care was taken to avoid any stasis and to collect it under oil. The blood was allowed to clot and then centrifugated. Determinations were then carried out on the serum. In a few experiments, determinations were made on the whole blood. The dog was then placed in a wooden crate of suitable size and placed between the plates of the condenser. In some cases the exposures were made for only short periods of thirty minutes, and in other cases they varied from thirty minutes up to as long as twelve hours. The rate of heating of the animal is dependent to a certain extent on the distance between the plates and on how much of the area between the plates is filled up by the animal. Several experiments have been carried out in which the dog was heated rapidly within half an hour to temperatures of from 42.5 to 43 C. In other experiments, the dogs were brought up to a certain temperature in from thirty to sixty minutes, and attempts were made to keep them at that temperature for varying periods of time. It would have been desirable in all these experiments to have control over the temperature and humidity of the room during the treatment, but this was not possible.

The volume of blood was determined by dye blood volume method of Hooper, Smith, Belt and Whipple,[8] brilliant vital red being used. Cell volumes were determined in duplicate with the Van Allen [9] hematocrit, 1.6 per cent sodium oxalate solution as diluent being used. The improved Newcomer [10] method was used in the estimation of hemoglobin. For p_H, the quinhydrone procedure of Cullen [11] was used on serum. The p_H values were determined at room temperature and calculated to 38 C. (using the calculation $p_{H_t'} = p_{H_t} - (0.01 \times [t'\text{-}t])$ Carbon dioxide was determined by the Van Slyke and Neill [12] manometric

7. Cowgill, G. R.: J. Biol. Chem. **56**:725, 1923.

8. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Am. J. Physiol. **51**:205, 1920.

9. Van Allen, C. W.: J. Lab. & Clin. Med. **10**:1027, 1925.

10. Newcomer, H. S.: Biol. Chem. **37**:465, 1919; **55**:569, 1923.

11. Cullen, G. E., and Beilmann, E.: J. Biol. Chem. **64**:727, 1925. Cullen, G. E., and Earle, I. P.: J. Biol. Chem. **61**:523, 1928.

12. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. **61**:523, 1924.

TABLE 1.—*Data on High Frequency Treatment of Dogs*

Date, 1929	Dog	Total Exposure, Hours	Rectal Temperature, C.		Average Temperature, C.	Maintained, Hours	Cell Volume, per Cent	p_H (38 C.)	Inorganic Phosphorus, Milliequivalents	Total Protein, Milliequivalents	Bicarbonate, Milliequivalents	Chloride, Milliequivalents	Lactic Acid, Milliequivalents	Total Base, Milliequivalents	Nonprotein Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Red Blood Cells, Millions	White Blood Cells, Thousands	Differential White Count				Comment
			Before and After	Maximum																Neutrophils	Eosinophils	Monocytes	Lymphocytes	
3/ 1	23*	0	38.6	....	....	...	38.0	7.32	2.20	33.8	8.7	87.2	5.8	126	27.9	98	10.4	8.44	10.1	83.0	4.0	7.0	6.0	
		4½	40.0	40.0	39.7	4	43.0	7.30	2.44	40.2	7.6	90.6	5.5	125	32.1	96	11.1	8.14	14.4	94.0	1.0	3.0	2.0	
3/ 4	23*	0	38.9	....	....	...	38.0	7.37	2.30	46.9	8.2	90.6	3.3	135	29.7	99	9.7	6.18	5.4	81.0	6.0	5.0	8.0	
		5	41.5	41.6	41.0	3	43.0	7.38	1.33	53.6	5.5	90.6	6.2	126	45.1	104	10.9	7.52	10.9	93.0	...	7.0	....	
		0	38.0	....	....	...	38.7	7.38	2.61	45.5	....	85.5	3.9	...	45.5	100	8.9	6.65	9.2	88.0	...	12.0	....	1½ hours after treating
3/ 8	..	0	....	....	....	...	34.5	7.36	2.08	37.6	10.2	80.4	2.6	108	25.2	91	10.0	5.11	8.9	75.0	...	19.0	6.0	3 days later
3/ 8	23*	0	39.2	....	....	...	38.0	7.39	2.55	36.8	17.7	83.8	2.7	141	24.4	105	10.6	6.11	16.5	58.0	1.0	31.0	10.0	
		6½	42.2	42.2	41.2	5	49.0	6.95	2.78	30.8	5.2	92.3	10.8	136	64.5	149	13.3	8.14	20.3	67.0	...	16.0	4.5	Died 1½ hours after treatment
3/15	24	0	39.2	....	....	...	43.0	7.28	1.63	16.7	14.9	115.0	9.3	136	28.0	...	10.3	8.03	27.3	80.0	4.5	2.5	11.5	
		3	42.9	43.3	42.3	2½	54.0	7.14	3.32	26.0	11.1	117.0	....	147	85.8	151	11.4	8.36	10.4	79.0	0.5	4.5	7.0	Died 30 minutes after treatment, 20 nucleated reds to 200
3/25	25	0	39.0	....	....	...	36.0	7.23	4.37	12.6	14.6	120.0	....	148	26.6	134	12 2	6.41	9.7	59.0	5.0	3.5	32.5	
		5	41.7	41.7	41.1	3	36.0	7.25	4.68	13.5	13.0	133.0	....	162	33.8	123	....	5.98	21.8	74.0	...	11.0	14.0	
3/29	25	0	39.1	....	....	...	32.0	7.28	4.48	13.1	14.2	115.0	....	183	29.6	134	11.1	7.01	7.3	53.0	3.0	8.0	36.0	
		4¾	41.9	42.5	41.1	3	37.5	7.23	3.73	15.8	12.7	137.0	....	203	87.0	...	....	7.27	12.4	82.0	1.0	7.0	7.0	
4/ 5	25	0	39.0	....	....	...	38.5	7.32	5.56	16.5	15.8	108.0	5.5	170	30.9	145	10.8	6.09	8.5	63.0	4.5	9.0	22.5	
		4	43.3	43.3	41.8	4	46.0	7.23	2.54	19.0	11.1	131.0	11.9	199	66.0	86	12.9	6.57	26.0	80.0	...	1.5	18.5	
		0	38.4	....	....	...	44.0	7.32	4.36	15.1	17.0	113.0	3.9	176	57.6	121	11.5	....	....	....	...	....	....	2 hours later
4/ 8	25	0	39.6	....	....	...	28.0	7.32	3.90	11.7	18.2	108.0	2.8	163	30.0	124	12.6	5.28	9.8	57.0	3.0	6.0	31.0	3 days later
		0	39.2	....	....	...	24.0	7.39	4.13	12.7	18.0	113.0	3.4	160	20.0	120	13.5	4.42	11.0	75.0	0.5	3.0	21.5	3½ hours in crate without treatment
4/12	25	0	39.1	....	....	...	27.0	7.26	4.33	16.0	15.6	112.0	....	135	32.8	148	10.6	4.66	10.8	70.0	...	11.0	19.0	
		4	42.8	42.8	41.9	3½	....	7.24	2.06	15.1	11.4	129.0	....	165	73.0	161	15.3	5.58	28.8	87.0	...	9.0	4.0	3 nucleated reds to 200
7/ 8	25	2	39.5	....	....	...	46.0	7.28	4.00	13.7	15.9	107.0	6.2	153	30.8	120	....	9.12	8.3	29.0	3.0	2.0	66.0	
			43.5	43.5	....	...	53.0	7.28	3.42	14.2	11.0	110.0	13.5	148	58.8	67	....	10.7	57.8	53.0	3.0	4.0	46.0	Died 50 minutes after treatment, 12 nucleated reds to 200
4/ 1	26	0	40.0	....	....	...	49.0	7.45	4.35	17.2	22.1	118.0	12.6	200	27.5	101	....	....	....	....	...	....	....	Struggled considerably before and during treatment
		2	43.4	43.9	....	2	53.0	7.43	2.54	....	11.6	126.0	20.0	202	58.1	79	11.9	8.61	10.5	73.0	3.0	3.0	36.0	Died 10 minutes after treatment, 35 nucleated reds to 200
4/22	27	0	39.4	.. .	....	...	45.0	7.29	2.95	17.0	16.0	118.0	....	163	42.2	131	....	7.46	19.6	80.0	1.0	8.0	5.0	
		2	43.4	43.4	42.2+	2	56.0	7.21	3.19	30.2	4.38	132.0	....	174	33.8	185	....	8.76	15.4	90.0	...	3.0	4.0	Died 15 minutes after treatment, 7 nucleated reds to 200

4/26	28	0	39.0	....	....	...	42.0	7.32	2.53	12.9	18.5	112.0	....	155	28.4	...	....	8.03	7.1	69.0	2.0	4.0	25.0	
		5¼	41.7	41.9	40.5+	5	57.0	7.38	1.16	13.0	14.8	128.0	....	163	45.0	109	12.2	9.10	17.8	92.0	...	3.0	3.0	Struggled considerably during treatment
5/17	28	0	39.2	....	....	...	34.0	7.25	2.27	15.2	14.9	114.0	4.8	147	30.6	104	10.8	7.20	16.0	86.0	...	4.0	10.0	
		½	46.0	46.0	41.7+	½	....	6.80	3.18	18.5	5.2	115.0	23.4	160	48.8	290	11.3	....	....	....	...	....	....	Died 10 minutes after treatment, struggled considerably
5/20	29	0	39.2	....	....	...	40.8	7.35	2.48	17.1	16.9	103.0	3.5	143	30.1	141	12.5	8.02	9.6	69.0	6.0	3.0	22.0	
		½	41.4	41.4	....	...	41.0	7.45	1.53	19.8	14.4	106.0	8.7	154	28.7	145	11.1	7.63	8.8	65.0	4.0	3.0	27.5	
5/24	29	0	38.2	....	....	...	40.6	7.36	2.42	19.9	16.0	112.0	5.6	146	39.4	133	12.5	7.28	9.2	55.0	4.5	1.0	36.5	
		½	41.5	41.5	....	...	43.3	7.41	1.81	16.0	14.5	112.0	9.6	142	43.0	180	11.1	7.12	10.1	50.5	3.5	....	43.0	
6/13	29	0	38.4	....	....	...	50.0	7.32	2.43	12.0	18.1	109.0	4.0	143	41.0	132	10.8	7.98	10.4	67.0	3.0	4.0	26.0	
		4½	43.9	43.9	40.6+	3	54.0	7.22	2.30	23.2	13.2	109.0	2.3	...	92.4	135	13.5	9.73	13.4	85.5	1.0	3.0	7.5	Died 15 minutes after treatment, 5 nucleated reds to 200
5/29	31	0	39.0	....	....	...	43.5	7.23	2.96	17.0	17.9	105.0	....	143	33.5	127	12.6	5.86	13.1	69.0	3.0	11.0	17.0	
		½	43.2	43.2	....	...	....	6.97	2.97	13.6	8.8	105.0	25.8	140	57.0	222	11.6	7.79	27.8	64.0	2.5	8.5	23.0	Died 7 minutes after treatment, 9 nucleated reds to 200, struggled considerably
5/31	30	0	39.0	....	....	...	38.2	7.16	3.21	10.0	15.4	106.0	....	158	21.2	160	....	6.32	9.2	62.0	1.0	15.0	21.0	Dog 6 months old, 20 nucleated reds to 200
		½	41.3	41.3	....	...	....	7.24	1.88	13.1	10.9	109.0	....	156	29.5	189	....	7.00	10.4	81.0	...	12.0	2.0	39 nucleated reds to 200
6/ 4	30	0	37.9	....	....	...	38.2	7.38	1.62	11.4	14.9	109.0	3.5	147	34.1	164	12.1	6.83	10.1	58.5	4.0	7.5	28.0	27 nucleated reds to 200
		4½	41.5	41.5	41.1+	4	....	7.30	1.56	14.3	12.9	104.0	10.3	143	57.0	139	12.3	7.74	52.0	84.0	6.5	5.0	4.5	29 nucleated reds to 200
6/11	30	0	39.0	....	....	...	30.0	7.22	2.88	11.5	17.1	106.0	....	147	27.0	126	11.6	5.22	20.2	71.0	3.0	11.0	12.0	22 nucleated reds to 200
		3½	43.3	43.5	41.1+	3	....	7.15	2.53	11.3	12.9	107.0	12.3	160	65.2	38	13.2	....	....	....	...	....	....	Died 10 minutes after treatment
6/ 6	34	0	38.9	....	....	...	46.0	7.39	2.38	11.2	15.3	107.0	....	147	22.3	154	11.6	6.83	12.1	49.0	28.0	2.0	21.0	
		12	42.2	43.1	40.6	11½	56.0	7.31	3.54	16.4	11.9	99.2	....	...	88.2	123	12.6	9.47	58.0	86.0	1.0	5.0	3.0	
6/17	33	0	39.2	....	....	...	36.0	7.28	3.48	13.7	15.0	108.0	....	164	56.0	146	13.3	8.00	8.5	53.0	15.0	3.0	29.0	Dog 7 months old
		6	40.6	42.3	40.6	5	51.5	7.18	4.64	16.1	12.7	112.0	....	177	117.0	182	13.4	9.00	61.2	89.0	1.0	2.0	4.0	Died from 10 to 12 minutes after treatment
6/20	35	0	38.9	....	....	...	34.0	7.33	3.24	12.8	15.0	106.0	....	150	38.0	135	10.5	5.85	5.8	47.0	6.0	10.0	35.0	
		5	41.5	42.3	41.1	4	53.5	7.01	4.24	10.4	7.0	111.0	....	148	81.0	248	10.7	9.90	16.4	77.0	1.0	9.0	11.0	Died 30 minutes after treatment
6/27	32	0	39.0	....	....	...	38.5	7.36	3.20	12.6	15.1	112.0	....	145	42.5	73	13.3	6.53	6.8	66.0	4.5	6.0	23.5	
		5	41.5	42.4	41.1+	2	42.5	7.37	3.66	11.0	15.7	106.0	....	156	38.7	96	12.5	6.88	28.4	93.0	...	3.0	4.0	
7/ 1	32	0	39.3	....	....	...	34.5	7.28	3.50	15.8	16.6	113.0	3.0	149	38.2	95	12.7	6.19	13.1	73.5	1.5	7.0	18.0	
		5	41.3	42.1	41.1+	5	34.5	7.19	3.52	10.3	15.2	109.0	4.3	145	36.3	82	9.8	6.52	26.8	82.5	1.0	4.0	9.5	
7/ 2	36	0	38.9	....	....	...	38.0	7.34	2.26	15.7	17.1	104.0	3.1	149	21.7	115	12.5	8.19	9.8	84.0	1.0	5.0	10.0	
		6	40.3	40.8	40.0+	5¼	40.0	7.32	1.62	16.6	12.5	110.0	3.2	154	22.1	127	13.5	7.92	15.5	....	...	....	....	
7/11	36	0	38.8	....	....	...	33.0	7.35	1.91	15.1	17.8	110.0	4.9	151	20.0	116	12.2	6.66	14.0	78.0	...	5.0	15.0	
		5½	40.5	41.0	40.5+	5¼	40.0	7.31	1.16	14.8	15.3	110.0	9.0	148	22.4	135	10.6	7.44	16.4	92.0	...	4.0	4.0	
7/15	36	0	38.7	....	....	...	37.0	7.36	2.14	19.0	16.3	103.0	3.7	143	19.0	116	12.5	8.30	18.6	83.0	...	6.0	11.0	
		5¾	42.0	42.0	40.6	5¼	43.5	7.28	1.16	18.9	8.3	106.0	14.0	142	26.4	160	14.0	9.15	26.4	94.0	...	2.0	11.0	
7/19	36	0	38.9	....	....	...	35.0	7.21	2.50	15.0	16.7	104.0	3.4	147	17.5	107	11.0	7.02	12.0	81.0	2.0	7.0	10.0	
		5½	41.0	41.7	41.0+	5	38.5	7.23	1.45	16.6	13.6	109.0	5.2	147	21.0	129	10.6	7.36	15.2	94.0	...	2.0	4.0	
7/17	37	0	39.3	....	....	...	39.0	7.31	3.54	13.0	16.3	105.0	....	156	35.7	130	13.1	8.03	9.0	60.0	3.0	7.0	30.0	
		5½	41.0	41.6	41.0+	5	37.5	7.36	3.02	11.8	13.6	104.0	....	150	44.1	132	11.3	7.02	13.8	88.0	...	6.0	5.0	

* Determinations on whole blood except p_H and calcium.

method. Base present as bicarbonate was calculated in millimols by use of the following equation [13] where carbon dioxide represents the per cent by volume of carbon dioxide content.

$$B_{HCO_3} = \frac{CO_2 - \left(\frac{14.04}{\text{antilog } (p_H\ 6.1)} \times 0.713\right)}{2.24}$$

Nonprotein nitrogen and sugar were estimated by the Folin-Wu [14] procedure. Inorganic phosphates were determined by the method of Fiske and Subbarow [15] and calculated to milliequivalents of phosphorus per liter by multiplying the milligrams per hundred cubic centimeters by the factor $\frac{18}{31.04}$. Clark and Collip's [16] modification of the Kramer-Tisdall method was used for calcium. Lactic acid was estimated by the method of Friedemann, Cotonio and Shaffer,[17] the condenser unit of Davenport and Cotonio [18] being used. By dividing the milligrams per hundred cubic centimeters by 9, the lactic acid was converted to milliequivalents.

For total base the micromethod of Stadie and Ross [19] was used. Chlorides were determined by the Whitehorn [20] method and were calculated to milliequivalents by dividing the milligrams per hundred cubic centimeters by 5.85. Total blood proteins were determined by a micro-Kjeldahl method with direct nesslerization. The more recent equation of Van Slyke and associates [21] for the base combining power of the total protein of serums were used. Assuming a ratio of albumin: globulin as 1.8:1, it is $B_p = 1.072\ P_T\ (p_H - 5.04)$.[22]

RESULTS AND COMMENTS

The total number of experiments that were carried out together with the experimental data obtained are indicated in table 1.

Effect of High Frequency Heating on the Animal.—Animals placed in the high frequency field showed considerable variation in their response to any given quantity of current, some being more restive than others. That the humidity and the temperature of the room had an effect was noticeable from the fact that on warm humid days in the summer, animals were found to heat up much more rapidly. The heating effect was felt almost as soon as the current was turned on and dogs

13. Peters, J. P.; Bulger, H. A.; Eiseman, A. J., and Lee, C.: J. Biol. Chem. **67**:141, 1926.

14. Folin, O., and Wu, H.: J. Biol. Chem. **38**:81, 1919.

15. Fiske, C., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.

16. Clark, E. P., and Collip, J. B.: J. Biol. Chem. **63**:461, 1925.

17. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: J. Biol. Chem. **73**: 335, 1927.

18. Davenport, H. A., and Cotonio, M.: J. Biol. Chem. **73**:359, 1927.

19. Stadie, W. C., and Ross, E. G.: J. Biol. Chem. **65**:735, 1925.

20. Whitehorn, J. C.: J. Biol. Chem. **65**:449, 1925.

21. Van Slyke, D. D.; Hastings, A. B.; Miller, A., and Sendroy, J.: J. Biol. Chem. **79**:769, 1928.

22. Peters, J. P.; Wakeman, A. M.; Eiseman, A. J., and Lee, C.: J. Clin. Investigation **6**:517, 1929.

would usually begin to pant within two or three minutes after starting the experiment. In general, it was noticed that animals were more irritable while their temperature was being raised; maintenance or reduction of temperature from higher levels did not materially affect the animal. The respiratory movements in most cases became extremely rapid and were maintained at a high rate for varying periods after the treatment. In some of the longer experiments in which the temperatures were above 42.6 C. and death the usual result, it was noticed that after the very rapid respiration it became shallow and weak, and finally the animal died of respiratory failure. The dogs heated to high temperatures frequently developed diarrhea, and in some instances abdominal cramps were noticeable. There was always evidence of intense fatigue.

Some of the dogs made efforts to escape from the crate, while others were quite placid. It was observed that animals reacted to increased current by increase in the rate of rise in temperature up to a certain point, about 42 C. At this point, the organism showed a definite resistance to increased temperature. Finally, the mechanism for the elimination of heat would break down, after which an increase in the rate of temperature rise would occur. Great care is necessary when heating above this critical point. Flinn and Scott [23] and Henderson and Haggard [24] have noted similar physiologic limitations. A reflection of this great resistance to change in temperature at this critical point is seen in the values for the carbon dioxide content.

In the production of artificial fever by this method, it is of interest to know how long the fever is maintained. When animals were heated to a temperature of from 41 to 42 C., it was noticed that return to normal temperature occurred within about thirty minutes. With higher temperature, from 42 to 43 C., the return to normal was usually slower varying from sixty minutes to two hours. In a few instances with the higher temperature, the animals either died shortly after treatment or did not return to normal temperature and died within a few hours of treatment.

The pathologic changes produced in the tissues of these heated animals is discussed in detail in a paper by Jacobson and Hosoi.[25]

Effect of High Frequency Treatment On the Blood Volume, Cell Volume, Hemoglobin and Weight.—In the consideration of the effect of high frequency treatment, it is necessary to consider not only the total period of heating and the average or maximum temperature, but also the rate of heating. Table 2 gives results of several experiments in which

23. Flinn, F. B., and Scott, E. L.: Am. J. Physiol. **66**:191, 1923.

24. Henderson, Y., and Haggard, H. W.: J. Biol. Chem. **33**:333, 1918.

25. Jacobsen, V. C., and Hosoi, K.: The Morphologic Changes in Animal Tissue Due to Heating by an Ultrahigh Frequency Oscillator, this issue, p. 744.

the animals were heated to various average temperatures for different periods of time. It is seen that in those animals which were not allowed water during the treatment that the percentage of loss in weight varies with the length and intensity of treatment, the loss in weight in some of the experiments amounting to as high as from 10 to 11 per cent. The loss in weight is undoubtedly due largely to loss of water through the lungs by hyperventilation. Whenever the animals were given water to drink, the percentage of loss in weight was greatly reduced. The animals usually regained their original weight in twenty-four hours.

TABLE 2.—*Effect of High Frequency Treatment on Blood Volume, Cell Volume, Hemoglobin and Weight*

				Weight			Blood Volume			Cell Volume			Hemoglobin		
Date, 1929	Dog	Total Exposure, Hours	Maximum Rectal Temperature, C.	Before, Kg.	After, Kg.	Loss, per Cent	Before, Cc.	After, Cc.	Decrease, per Cent	Before, per Cent	After, per Cent	Change, per Cent	Before, per Cent	After, per Cent	Change, per Cent
3/ 1	23*	4½	40.0	15.10	.....	....	1,680	1,400	16.5	38.0	43.0	+13.0	.....	.....	.....
3/ 4	23*	5	41.5	14.88	13.71	7.9	.....	.....	....	38.0	43.0	+13.0	.....	.....	.....
3/15	24*	3	43.3	9.58	8.87	7.4	681	423	24.9	43.0	54.0	+25.6	.....	.....	.....
3/25	25*	4½	41.7	10.48	9.74	6.9	.....	.....	....	36.0	36.0	0	.....	.....	.....
3/29	25*	4¾	42.5	10.48	9.45	9.8	.....	.....	....	32.0	37.5	+17.0	.....	.....	.....
4/ 5	25*	4	43.0	10.78	9.75	9.6	919	694	24.5	38.5	46.0	+19.5	.....	.....	.....
4/12	25*	4	42.8	10.97	9.97	10.0	.....	.....	....	....	....	.....	.....	.....	.....
4/26	28*	5¼	41.7	9.05	8.04	11.1	.....	.....	....	42.0	57.0	+35.0	12.35	19.06	+62.0
5/ 1	28*	3½	42.2	8.20	7.81	4.8	.....	.....	....	....	....	.....	.....	.....	.....
5/20	29*	½	41.4	15.00	14.65	2.3	.....	.....	....	40.8	41.0	+ 0.5	14.03	14.38	+ 2.5
5/24	29*	½	41.5	15.70	15.40	1.9	1,235	1,110	9.9	40.6	43.3	+ 6.6	14.26	14.87	+ 4.3
6/ 4	30†	4½	41.6	7.90	7.65	3.2	.....	.....	....	....	....	.....	.....	.....	.....
6/ 6	34†	12	43.1	13.70	13.40	2.2	1,250	1,055	21.8	41.0	56.0	+21.0	13.29	20.60	+55.0
6/17	33†	6	42.3	10.20	9.48	7.0	.....	.....	....	....	....	.....	13.40	14.50	+12.0
6/20	35†	5	42.3	10.10	9.70	4.0	.....	.....	....	34.0	53.5	+57.0	12.18	14.61	+20.0
6/27	32†	5	42.1	14.70	14.48	2.2	1,162	1,012	12.9	38.5	42.5	+10.4	12.99	14.26	+10.5
7/ 1	32†	5	42.1	14.30	13.77	3.6	.....	.....	....	34.5	34.5	0	12.44	12.62	+ 1.4
7/ 2	36†	6	40.8	13.77	13.44	2.4	945	908	3.9	38.0	40.0	+ 5.2	14.61	15.53	+ 6.3
7/ 8	25†	2	43.7	15.30	14.88	2.7	.....	.....	....	46.0	53.0	+15.2	16.7	17.53	+ 5.0
7/11	36†	5¼	41.1	13.20	12.94	2.0	970	870	10.3	33.0	40.0	+21.2	.....	.....	.....
7/15	36†	5¾	42.0	12.70	12.30	3.2	869	783	9.9	37.0	43.5	+17.5	12.99	13.81	+ 6.3
7/19	36†	5½	41.7	12.30	12.00	2.3	.....	.....	....	35.0	38.5	+10.0	11.39	11.69	+ 2.6

* No water during treatment.
† Water during treatment.

This excessive loss in water is apparently responsible for the decrease of blood volume. In all of our experiments in which the blood volume was measured, there was a decrease in volume varying from 3 to 25 per cent. The concentration of the blood is also evidenced by the increase in cell volume and hemoglobin, which runs somewhat parallel with the decrease in blood volume. These results are in line with those of Flinn and Scott,[23] who found that there was blood concentration in dogs on exposure to extreme heat. At high temperature, the rate of replacement of water cannot keep pace with the rate of the loss, and a certain amount of concentration results. The concentration of blood can apparently be reduced as much as 25 per cent with recovery of the animal to normal condition.

Effect of High Frequency Treatment on the Acid Base Equilibrium of the Blood.—In order to obtain a better idea of the changes brought about by high frequency heating, a tabulated summary of most of the experiments listed in table 1 has been prepared. First of all we have taken the values obtained before treatment on twenty-four experiments and determined the averaged values. The experiments were divided into two main groups, those heated for one-half hour and those heated from two to six hours. In the short periods there is one series of three experiments in which dogs were heated to a maximum rectal temperature of 41.7 C. and in a second series of two experiments they were heated to 43.2 and 46.C., respectively. Both of these dogs died within fifteen minutes after the treatment. In the longer periods of treatment, we divided the experiments into three series. In the first series there are seven experiments in which the maximum temperature was between 41.1 and 41.7 C., another series of six experiments in which the temperature was brought up to from 42.2 to 42.8 C. and a third series of six experiments with a maximum temperature of 43.3-44.+C. In this third series only one of the six dogs recovered after the treatment; the remainder died within an hour. The averaged values for each of these series of experiments are given in table 3.

The rise in temperature of the animal causes a marked hyperpnea, and as a result there is a great washing out of carbon dioxide, and the bicarbonate content of the blood is consequently reduced. This reduction of bicarbonate bears a direct relation to the rate of heating and temperature attained. It is most marked in the short rapid period of heating with high temperature of from 43 to 44 C., in which series of experiments the bicarbonate was reduced to the low level of 7 millimols. According to Haggard,[26] Koehler,[27] and others,[28] such changes with hyperpnea in man result in an increase in p_H. Flinn and Scott[23] have also noted that exposure of dogs to environmental temperature above 40 C. results in a marked increase of p_H.

In none of our experiments was a distinct alkalosis noted, although a tendency in that direction is indicated in the three experiments of one-half hour treatment with a maximum temperature of 41.7 C. In this series of experiments, the p_H showed an average increase of 0.07. It may be that a greater alkalosis was not indicated due to the production of lactic acid which is almost doubled in this series over the values before

26. Haggard, H. W.: J. Biol. Chem. **44**:131, 1920.

27. Koehler, A. E.: Arch. Int. Med. **31**:590, 1923.
1923.

28. Cajori, J. A.; Crouter, C. Y., and Pemberton, R.: J. Biol. Chem. **57**:217, 1923.

heating. In the two experiments in which the animals were brought up to a temperature of 43.2 C. and 46 C. within half an hour, the p_H was greatly reduced, indicating a marked acidosis. The average p_H for this series was 6.89, which is on the acid side of neutrality. This marked acidosis would be sufficient to account for the death of these animals. It is also of interest to note that the lactic acid is increased in these experiments to more than five times the values before treatment. These observations are comparable with those of Austin, Sunderman, and Camack [29] on cold-blooded animals. They observed that with an increase of from 15 to 20 C. change in the environment of alligators, there results a lowering of p_H and formation of considerable amounts of lactic acid.

TABLE 3.—*Tabulated Summary of High Frequency Experiments on Dogs; Averaged Values*

High Frequency Exposure	Number of Experiments Averaged	Maximum Temperature, C.	p_H at 38 C.	Inorganic Phosphorus, Milliequivalent	Total Proteins, Milliequivalent	Sodium Bicarbonate, Milliequivalent	Chloride, Milliequivalent	Lactic Acid, Milliequivalent	Total Acid, Milliequivalent Columns 4+5+6+7+8	Total Base, Milliequivalent	Nonprotein Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
Before treatment	25	39.0*	7.30	3.04	14.8	16.4	110	4.6†	149	153	30.8	120	11.9
½ hr. treatment..	3	41.7	7.37	1.74	16.3	13.3	109	9.3	150	151	33.7	171	11.6
½ hr. treatment..	2	43.3+	6.89	3.07	16.0	7.0	110	24.6	161	153	52.9	256	11.5
4-6 hrs. treatment	7	41.1-41.7	7.31	1.89	14.9	13.8	118	5.8	154	155	28.9	125	11.8
4-6 hrs. treatment	6	42.2-42.8	7.21	3.49	13.7	11.9	113	9.2‡	151	162	64.4	154	11.9
2-4½ hrs. treatment	6	43.3-44+	7.24	2.92	20.1	10.3	120	14.4	168	175	61.2	125	11.7

* Average temperature before treatment.
† Average of thirteen normals.
‡ Average of two experiments only.

In these short rapid periods of heating, the animal has no chance to compensate appreciably for the changes brought about, and the effects of temperature per se on biologic functions are observed.

The longer periods of heating do not show any striking changes in p_H although with dogs heated above 42 C. there is a tendency toward acidosis. The lactic acid is also greatly increased in these series of experiments. The increase in lactic acid is probably due to the fact that as a result of a rise in temperature, metabolism is greatly increased resulting in a tissue anoxemia. Also it may be that lactic acid is augmented to some extent by the increased muscular activity in those dogs which resisted treatment.

29. Austin, J. H.; Sunderman, F. W., and Camack, J. G.: J. Biol. Chem. **72:** 677, 1927.

The chloride is not significantly affected by the high frequency treatment. In a few experiments the chloride is increased from 10 to 15 per cent, but these changes can be accounted for by the blood concentration. In the averaged values in table 3, the only significant change in chloride is in the last series of experiments in which the animals were heated from 43 to 44 C. for periods of from two to four hours.

The total proteins tend to be slightly increased in the majority of experiments. This may be the result of blood concentration, and undoubtedly is the explanation for the marked increase in the last series of experiments with temperatures of from 43 to 44 C.

The changes in inorganic phosphorus in the blood were somewhat variable. In the short and long periods of treatment with maximum temperature of 41.7 C., there is a marked reduction of from 25 to 35 per cent for the averaged values. With the higher temperatures, the averaged values are not significantly changed. It is difficult to associate the changes in inorganic phosphorus in these experiments with any definite mechanism.

The total base content of the serum does not seem to be particularly affected except in the long periods with temperatures above 42 C., in which experiments there is a small increase. These changes can be accounted for by the dehydration with subsequent concentration of the blood. The calcium is not appreciably altered, as is indicated by averaged values for this series of experiments.

Effect of High Frequency Heating on the Nitrogenous Constituents and Sugar of the Blood.— The general effect of high frequency heating is to bring about an increase in nonprotein nitrogen in the blood. In the short period of heating with a maximum temperature of 41.7 C., it will be noted from table 3 that there is an increase of about 10 per cent in nonprotein nitrogen, while with the higher temperature of 43.3 + C., the averaged value shows an increase of 75 per cent. In the longer periods of treatment, the nonprotein nitrogen is still further increased. The averaged values for temperatures above 42 C. show an increase over 100 per cent, and in several experiments the increase is over 200 per cent. An exception to this increase in nonprotein nitrogen seems to occur in the series of experiments in which the animals were treated from four to six hours and brought up to a temperature of from 41.1 to 41.6 C., However, the nonprotein nitrogen of the series before treatment is lower than the average for the whole series, and there is an increase for this series from 23 mg. before treatment to 28.9 mg. after treatment, or about 25 per cent.

Blood concentration may account for part of the increase in nonprotein nitrogen, but in many of the experiments the increase in nonpro-

tein nitrogen is all out of proportion to the blood concentration. Other contributing factors to this increase would be the increase of metabolism resulting from the rise in temperature. As pointed out by Du Bois,[30] metabolism follows the temperature law of Van't Hoff, which would mean that for every rise of 10 C. the rate of oxidation would be increased 2.5 times. With the rise in temperature an oliguria occurs, and the production of metabolites, which continues whether urine is excreted or not, results in an accumulation in excess in the body.

Several experiments have been carried out in which the urea, creatinine and amino-acid nitrogen have been determined to see whether any particular nitrogen component is responsible for this increase of

TABLE 4.—*Effect of High Frequency Treatment on the Nitrogenous Constituents of the Blood*

Date, 1929	Dog	Total Exposure, Hours	Rectal Temperature, C. Before and After Exposure	Rectal Temperature, C. Maximum	p_H (38 C.)	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Amino-Acid Nitrogen, Mg. per 100 Cc.
7/29	38	0	39.0	....	7.31	46.5	....	1.2	6.5
		1¾	43.6	43.6	7.16	158.0	....	1.3	13.5
7/30	39	0	39.4	....	7.33	30.3	20.8	1.8	5.2
		1½	43.6	43.6	7.15	88.0	48.4	2.3	12.4
7/31	40	0	38.7	....	7.41	19.7	14.7	1.1	7.7
		2½	43.3	43.3	7.35	42.9	30.2	1.7	8.5
8/ 2	37	0	39.3	....	7.41	24.9	17.1	1.5	7.6
		2¾	43.6	43.6	7.26	55.5	31.2	1.9	12.4
1930									
1/24	42	0	39.4	....	....	37.0	12.5	1.1	7.3
		3¼	40.6	40.8	....	48.8	23.6	1.3	7.2
1/28	42	0	39.4	....	....	42.0	....	1.6	7.9
		3	40.3	41.4	....	51.2	....	1.8	8.6
1/30	42	0	39.5	....	....	33.0	14.8	1.2	....
			40.2	40.5	....	46.5	31.0	1.2	....

nonprotein nitrogen. These experiments are listed in table 4. It will be noted that urea, creatinine and amino-acid nitrogen are increased along with the increase in nonprotein nitrogen. The urea nitrogen is increased somewhat parallel with the nonprotein nitrogen. In the more drastic heatings, the amino-acid nitrogen is increased along with the urea nitrogen and nonprotein nitrogen, while in the experiments with moderate heating the amino-acid nitrogen does not show much change. Creatinine is also increased in some of these experiments, although not in proportion to the other nitrogenous constituents. These experiments would indicate that the increase in nonprotein nitrogen is largely a result of increased metabolism with higher temperature.

The blood sugar content seems capable of considerable variation. We have found instances of considerable increase as well as decrease

30. Du Bois, E. F.: Basal Metabolism in Fever, J. A. M. A. **77**:352, 1921.

on exposure of animals to high frequency heating. In the short periods of heating, the increase in blood sugar is very marked. With a temperature of 43.3+ C., the average increase for the two short period experiments is 113 per cent. Even with a maximum temperature of 41.7 C., there is an average increase of 42 per cent. In the longer periods of treatment, the averaged values show only a slight increase in the series of experiments with temperatures from 42.2 to 42.8 C., the average increase for this series of experiments amounts to 28 per cent. In the series with temperatures of from 43.3 to 44.4 C., the average value shows a slight increase over the normal. However, on examining the individual experiments in this group, two of the experiments, those performed on

TABLE 5.—*Effect of High Frequency Heating on the Blood Sugar*

Date, 1929	Dog	Total Exposure, Minutes	Rectal Temperature, C.	p_H (38 C.)	Sugar, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.
10/25	41	0	39.4	7.35	118	38.0
		26	41.0	7.35	99	37.0
		50	42.2	7.40	98	....
		71	42.0	7.40	110	....
		94	41.9	7.40	130	....
		116	42.6	7.40	139	....
		133	43.5	7.25	264	65.0
11/2	42	0	40.0	7.40	117	53.0
		30	41.1	7.45	129	50.0
		66	41.1	7.45	137	63.0
		102	42.2	7.50	168	75.0
		140	43.0	7.50	196	74.0
11/11	42	0	39.4	7.40	93	43.0
		22	40.5	7.40	112	43.0
		52	41.5	7.40	149	52.0
		82	41.3	7.35	147	54.0
		112	42.2	7.40	157	60.0
		127	43.3	7.20	312	87.0

dog 24, March 15, and on dog 27, April 22, show an increase in blood sugar, while in the other four experiments of this series there is a great decrease in blood sugar. In the experiment of dog 30, June 11, the blood sugar was reduced to the low level of 35 mg.

Three experiments have been carried out in which we have studied the blood sugar concentration at various intervals during the period of treatment. These are listed in table 5. Along with these blood sugar determinations, the p_H and nonprotein nitrogen was also determined. In the first experiment of this series it will be noted that at first there is a temporary drop in blood sugar followed by a rise, and the greatest rise seems to occur with the change of p_H toward an acid condition. Within a period of seventeen minutes, the blood sugar rose from 139 to 264 mg. In the third experiment, there is also a great rise in blood sugar with the lowering of p_H. It is rather significant on examination of table 1 that the greatest increases in blood sugar occur in those experiments in

which the p_H has been lowered the most. These increases in blood sugar apparently are due first of all to the increase in metabolism resulting from a rise in body temperature and bringing about a mobilization and breakdown of glycogen. In changing of the blood to a more acid condition, the oxidation processes are slowed, resulting in much greater increases in blood sugar.

Effect of High Frequency Heating on the Numerical and Morphologic Changes in the Blood.[31]—Immediately after heating, there is usually a considerable increase in the number of red blood cells which may vary from 5 to 50 per cent. This is apparently associated with water loss as shown by the loss of weight, the decrease in blood volume, the increase in cell volume and the increase in hemoglobin. It may be in part a primary effect before compensation can take place due to fluid in the tissues becoming available in the circulation. There is, therefore, frequently more change after one or two hours' heating than is found after from four to six hours' heating.

In addition to the increased number of red cells, in many instances there is a marked increase in immature forms of red cells, notably normoblasts and red cells showing polychromatophilia, basic stippling and so-called Howell Jolly bodies. Many investigators [32] have noted that the peripheral blood of a large percentage of dogs normally contains nucleated red cells. We [33] have already stated that the changes in the blood of these animals suggested stimulation of the hemopoietic tissue, resulting, perhaps from anoxemia, or a mixing of blasts, formerly present, due to a more rapid circulation of blood. Erythropoiesis apparently was accelerated or at least immature red cells were delivered more rapidly to the peripheral blood, as indicated by the increased number of normoblasts, polychromatophilic cells and others showing nuclear fragments and basic stippling.

There is also a marked increase in the total white cells due to absolute and relative increase in the polymorphonuclear leukocytes. The lymphocytes and eosinophils are usually relatively markedly decreased. The change in the monocytes is less marked and less constant.

The number of red cells come back to normal more rapidly than do the white cells when the heating is continued for a long period or when the heating has been stopped.

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31. The Department of Medicine made the blood counts on most of our experimental animals, and Dr. Thomas Ordway wrote this section on blood.

32. Drinker, C. K.; Drinker, K. R., and Kreutzmann, Henry A.: J. Exper. Med. **27**:249, 383, 1918.

33. Ordway, Thomas; and Gorham, L. W.: Diseases of the Blood, Oxford Monographs, New York, Oxford University Press, 1928, vol. 9.

SUMMARY

The body temperature of dogs can be raised to any desired point by exposure to an ultrahigh frequency field. The temperature returns to normal quite rapidly unless the animal has been heated above 42 C. Animals heated above 42.5 C. for any great length of time do not survive treatment, although we have instances of an animal heated momentarily to 44.5 C. surviving.

Exposure of animals to an ultrahigh frequency field results in loss of weight, which is dependent somewhat on the length and intensity of treatment. There is also a decrease in blood volume amounting in some experiments to as much as 25 per cent. The concentration of the blood was also evidenced by the increase in cell volume and hemoglobin. Weight and blood volume usually return to normal within twenty-four hours

Raising the temperature of animals to 41.7 C. does not produce any great change in hydrogen ion content of the plasma, although there is a tendency toward a condition of alkalosis. With higher temperatures, the tendency is toward a condition of acidosis, apparently caused by great increase in the production of lactic acid. The increase in lactic acid is probably due to greatly increased tissue metabolism resulting in a tissue anoxemia. Changes in the chloride, total protein and total base are accounted for by the dehydration. Bicarbonate was greatly reduced, owing to excessive pulmonary ventilation with rise in body temperature. Changes in the inorganic phosphorus were somewhat variable, although with a maximum temperature to 41.7 C. there is a marked reduction.

Nonprotein nitrogen of the blood is generally increased; in some instances the increase is over 200 per cent. Urea nitrogen, creatinine and amino-acid nitrogen are also increased. These increases are accounted for by the increased metabolism resulting from rise in temperature and the oliguria.

The blood sugar content in most of the experiments shows an increase, in some cases amounting to as high as 150 per cent. The greatest increase in blood sugar occurs in those experiments in which the p_H has been lowered the most.

There is an increase in both red blood cells and total white cells. Besides the increase in red cells there is in many instances a marked increase in immature forms of red cells, suggesting a stimulation of the hemapoietic tissues.

THE MORPHOLOGIC CHANGES IN ANIMAL TISSUES DUE TO HEATING BY AN ULTRAHIGH FREQUENCY OSCILLATOR *

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Heat is a manifestation of normal cell metabolism which lends itself readily to measurement, and within the mammalian organism the limits between which cells can maintain life are fairly accurately known. The cell has probably an optimum temperature for the best performance of its duties, its temperature at a given moment being a function of the heat contributed by its neighbors, the degree of radiation from its own surface and the amount of heat generated by the metabolic activity within itself. Extremes of heat and cold are inimical to the normal activity of a cell or cell-composite, and the resultant degeneration or necrosis provides the chemical stimulus for the inflammatory reaction which in the broadest sense begins considerably before the appearance of a cellular exudate.

The body can withstand a much higher temperature than what is regarded as normal, and though a return to normal may follow hyperthermia, and even though a disease may apparently be arrested in its course by an application of heat, it does not alter the fact that many somatic cells have probably been destroyed or pathologically altered by the increased temperature. The more specialized cells of the body are the most sensitive to oxygen want and probably are the more profoundly affected by inflammatory irritants which, of course, include extremes of temperature. Hence in estimating the effects of a given method of applying external heat or of stimulating the internal production of heat, a careful experimental study of the functional and morphologic changes in the many types of tissue which make up the body must form the rational basis for any therapeutic applications.

The value of heat in the treatment of disease has been known since the dawn of medical history. The methods of application have been of exceedingly great variety, but almost without exception the heat has

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been applied externally, in dry or moist form, the temperature of the internal organs being raised largely by the passage of blood and lymph from the cutaneous field directly exposed to the heat source. The blood and lymph are thus the principal vehicles for the transportation of the heat much as is the fluid in a hot water heating circuit.

Since the therapeutic results of the use of external heat have been well established in a variety of conditions, a device capable of producing hyperthermia by increasing uniformly throughout the body heat production by the cells, would appear to offer a new approach to the experimental study of fever and possibly to increase the scope of therapy based on the febrile phenomenon.

Due to the rapid developments in the field of radio transmission, there has recently been devised in the research laboratory of the General Electric Company under the direction of Dr. W. R. Whitney, a high frequency alternating current heater or oscillator constructed on the principle of a short wave radio transmitter, except that the energy is concentrated between two plate electrodes instead of being directed from an aerial. Previously it had been noticed that when a workman was in the field of a short wave radio transmitter a rise of temperature of as much as 2.2 degrees developed in fifteen minutes, the height of the rise being determined by the time he remained in the field or by his proximity to the apparatus. A detailed description of the machine is to be found in the paper by Knudson and Schaible.[1]

A wave length of 25 meters was used in practically all the experiments, at an average of 2,000 volts, amperage from 0.2 to 0.35, oscillating about 10,000,000 per second. A temperature once reached could be maintained either by decreasing the voltage or by increasing the distance between the plate electrodes.

EXPERIMENTAL WORK

The animals used in this investigation were dogs, guinea-pigs and white rats, many given to us by Prof. Arthur Knudson after he had followed the chemical changes of the body fluids. Some animals were from Dr. C. M. Carpenter, who had studied them from a serologic point of view.

Twenty-three dogs were available, eleven of which were males and twelve females. They varied considerably in size and age and most of them were mongrels; three were German shepherd dogs. The breed of dog is probably unimportant although the amount of hairy coat might be worth noting. Four of the twenty-three dogs were long haired. The animals were apparently healthy at the beginning of the experiment.

Eleven dogs were given a single heating, but this involved removing the animal from the machine every thirty minutes to be weighed and to have its temperature taken, from four to seven minutes being required for these procedures. Eight dogs were heated from thirty-seven minutes to two hours and twenty minutes, one dog five and one-half hours, one dog six hours and one dog twelve hours.

1. Knudson, A., and Schaible, P., this issue, p. 729.

Protocol of Experiments with Dogs

Dog	Breed	Heatings	Total Heat	Normal Temperature	Maximum Temperature	Weight Loss, Kg.	Manner of Death	Time of Death After Heating	Time, P. M.	Complications
31	Hound	1	37 min.	102.7	109.8	....	Bled	0	30 min.	None
26	Terrier	1	1 hr. 20 min.	104.0	108.3	....	Bled	8 min.	2 hrs.	None
39	Police	1	1 hr. 30 min.	104.7	110.5	....	Died	6 min.	40 min.	None
27	Poodle	1	1 hr. 36 min.	103.0	109.4	....	Died	20 min.	4 hrs. 30 min.	None
38	Poodle	1	1 hr. 40 min.	103.0	110.5	....	Died	10 min.	25 min.	None
40	Hound	1	1 hr. 45 min.	101.7	110.0	0.85	Chloroformed	58 hrs.	0	None
7	Collie	1	2 hrs. 5 min.	102.8	111.0	....	Died	15 min.	1 hr.	None
41	Spaniel	1	2 hrs. 20 min.	103.8	110.0	....	Died	6 min.	13 min.	None
35	Bull	1	5 hrs. 15 min.	102.0	108.2	....	Died	40 min.	30 min.	None
33	Police	1	6 hrs.	102.6	108.0	....	Died	8 hrs.	6 hrs. 30 min.	None
34	Police	1	12 hrs.	102.0	109.6	....	Chloroformed	6 days	0	Skin burn
29	Bull	3	4 hrs. 50 min.	101.3	111.0	....	Died	14 min.	40 min.	Diaphragmatic hernia
37	Mongrel	2	8 hrs. 30 min.	102.8	110.6	0.3	Died	1 min.	35 min.	Skin burn
30	Hound	3	8 hrs. 40 min.	102.3	109.0	0.3	Died	10 min.	1 hr. 40 min.	Skin ulcers
21	Mongrel	3	8 hrs. 50 min.	101.6	108.7	....	Died	2 hrs.	1 hr. 30 min.	None
32	Police	2	10 hrs.	102.3	108.0	0.25	Chloroformed	8 days	0	Skin burn
28	Terrier	4	12 hrs. 23 min.	103.0	112.0	1.1	Died	1 min.	15 min.	Neck abscess
89	Spaniel	9	12 hrs. 40 min.	101.8	112.4	0.3	Died	0	0	None
23	Mongrel	3	15 hrs.	101.5	108.1	....	Died	15 min.	0	None
43	Hound	9	18 hrs.	102.2	108.0	0.4	Chloroformed	5 days	0	None
25	Collie	5	19 hrs.	102.3	110.6	0.1	Died	50 min.	1 hr. 15 min.	Anemia, skin burns
36	Bull	5	19 hrs. 30 min.	102.0	108.0	2.0	Died	6 min.	9 min.	Skin burns
44	Airedale	9	30 hrs. 20 min.	102.4	107.5	0.4	Chloroformed	1 hr.	0	Skin ulcer

The tissues were fixed in Zenker's fluid, 10 per cent neutral formaldehyde and absolute alcohol saturated with mercuric chloride for glycogen.

Eight dogs were given single heatings from thirty-seven minutes to two hours and twenty minutes. The maximum temperatures attained were nearly the same in all animals—the lowest 108.3 F., the highest 111 F. The lowest preheating temperature was 101.7 F., in dog 40 which was heated to 110 F., and the highest 104.7 F., in dog 39 whose temperature rose to 110.5 F.

The gross changes observed were few, congestion and edema being the most conspicuous. Rarely cloudy swelling of liver and kidneys was sufficiently marked to be seen with the naked eye. The microscopic alterations will be presented organ by organ.

The heart in five dogs showed acute congestion. Two, which did not show this change, died about the same time after the last heating as those which did. The third dog which showed no congestion died fifty-eight hours after the last heating, in ample time for the tissues to return to normal. Of these five dogs, two showed interstitial edema. Foci of hemorrhage were present in three dogs; one of them, dog 40, was killed with chloroform fifty-eight hours after the last heating. Dog 41, which died six minutes after heating, showed numerous glycogen granules in the muscle fibers. Fat droplets were demonstrated by scharlach r in dogs 38 and 40, a much greater amount in dog 38, which died ten minutes after heating, and in dog 40, killed fifty-eight hours afterward.

In six dogs there was acute congestion of the lungs but only one with alveolar edema. Emphysema was noted in four dogs. Three of these four also showed areas of atelectasis. Alveolar hemorrhage was found in dogs 39 and 41, hypersecretion of bronchial mucus in dog 31, and vacuolation of bronchial epithelium in 40.

In five dogs the spleen showed acute congestion and foci of hemorrhage in the pulp. In dogs 38, 39 and 41, there was necrosis of the lymphoid centers. Hemosiderin granules were present in dogs 26 and 31, and marked endothelial proliferation of the sinusoids in dogs 31 and 41. Dog 41 also showed diffuse fibrosis and adhesive perisplenitis.

None of this group showed congestion of the gastro-intestinal tract. Dog 26 showed a few mucosal hemorrhages in the ileum; dog 39, necrosis of the lymphoid centers in the ileum and hemorrhage in its mesentery, and dog 31, an excess of mucus in the stomach and colon.

Acute congestion of the liver was seen in all except dog 38; foci of hemorrhage in dogs 39 and 41, and focal necrosis in dogs 26, 38 and 39. Only in dog 40 was there definite cloudy swelling. Glycogen was present in dogs 30 and 41. Much fat was seen in dogs 34, 40 and 27, and was most abundant in the peripheral zones. The other dogs showed smaller amounts of fat.

The only noteworthy change in the pancreas was acute congestion. In dog 38, a lymph node attached showed germinal center necrosis and hemosiderin granules in the sinuses.

The kidneys were rather uniformly congested. There was cloudy swelling in six dogs and hydrops in four. Fat was present in most animals, the greatest amount in dog 38. Dogs 38 and 39 showed an old cortical scar. Glycogen was present in dogs 41 and 36.

The adrenals showed hemorrhages into the overlying fat in dogs 31, 39 and 40; congestion in dogs 38 and 39; increased fat droplets in dog 40, and focal hemorrhages and cortical degeneration in dogs 36 and 41.

There was congestion of the ovary in dog 31; otherwise it was normal.

The testes were normal except in dog 41, which showed exfoliation of the germinal epithelium and giant cells in the lumen of the tubules.

Dog 36 had a papillary adenocarcinoma of the breast, which showed nothing striking.

Some fatty infiltration and hydrops of the striated muscle were noted in dog 35, and glycogen in dogs 41 and 36.

The bone-marrow was active in all.

The thyroid was normal except in dogs 38 and 39, which had interstitial hemorrhages. There was no evidence of epithelial hyperplasia.

The salivary glands showed congestion.

There was congestion of the brain in all the dogs. Meningeal hemorrhages were seen in dog 26, chronic meningo-encephalitis in dog 40, focal hemorrhages in dog 38, and chromatolysis of the ganglion cells in dog 40.

In the cord chromatolysis of the anterior horn ganglion cells was noted in dog 40. This may have been a postmortem change.

Three dogs were given a single heating of over twice the duration of the former group: dog 35, five hours and fifteen minutes; dog 33, six hours, and dog 34, twelve hours. The normal and maximum temperatures for these animals were practically the same: 108.2, 108 and 109.6 F., respectively. Dog 35 died forty minutes after heating, dog 33 eight hours and dog 34 was killed with chloroform six days later. Dog 34 sustained several skin burns, which did not heal and became superficially infected.

There were no gross lesions in the organs of these dogs except congestion of the viscera.

Microscopically, the heart was congested, and in dog 35 there were focal hemorrhages deep in the myocardium. Scattered hyaline fibers were seen in dog 33, and in dog 34 there were foci of necrosis. No fat was present.

The lungs were congested and showed also small areas of atelectasis and emphysema but no edema. Dog 34 had patches of bronchopneumonia and some alveolar hemorrhage.

There was focal hemorrhage and necrosis of the lymphoid centers of the spleen in dogs 33 and 35; the latter showed marked endothelial proliferation.

Edema of the wall of the stomach was noted in dog 33. Congestion of the entire gastro-intestinal tract was seen in dog 35 with necrosis in the lymphoid tissue. Loss of Nissl's granules was noted in the ganglion cells of the intestine in dogs 33 and 35.

The liver was congested in all three dogs. Focal and central necrosis was noted in dog 33, and marked fatty infiltration in dog 35 with cloudy swelling.

In all three animals the kidneys showed congestion and cloudy swelling. Hydrops of the tubular epithelium was found in dog 34 with much fat in the tubular epithelium.

The adrenals were normal except that in dog 34 they showed some hemorrhage into the overlying fat.

The series of dogs which were heated more than once included twelve animals. Six were given from two to four exposures and from four hours and fifty minutes to twelve hours and twenty-three minutes. The rise in temperature varied from 6.4 to 8.7 degrees. Of these dogs, five died from one minute to two hours after the last heating, and one was killed eight days after the final heating. Dog 29 heated four hours and fifty minutes was found at necropsy to have a diaphragmatic hernia. Four developed severe skin burns (fig. 1) and one, dog 28, heated over twelve hours, had a large abscess of the neck.

The tissue changes of this group are of much the same order as those in the first group. The organs were congested, but since all but one dog died during the heating, this was probably an acute effect. Cloudy swelling was much less in evidence in the parenchymatous organs. Fatty metamorphosis was also less conspicuous. Glycogen content of liver, kidneys and muscle showed variation, and no conclusions can be drawn except that there was possibly a tendency toward depletion. Dog 89, heated nine times, a total of twelve and one-half hours, showed focal necrosis of the liver, fatty degeneration of the gastric muscle and hemorrhages in the mucosa of the intestinal tract.

Dog 43, given nine heatings, a total of eighteen hours, showed hemorrhages in the adrenals, increased fat in the renal epithelium and megakaryocytes in the splenic pulp. Dog 25 had severe skin burns and anemia and showed foci of rarefaction in the brain. It also had focal bronchopneumonia, hence caution must be used in estimating the effects of the heating.

Fig. 1.—The axillary region of dog 32 heated twice for a total of ten hours. Due to arcing in a moist surface, a "burn" was produced followed by sloughing in the area shown.

Dog 36, a female bulldog, was given five heatings for a total of nineteen and one-half hours. Several skin burns developed due to arcing, and the dog died six minutes after the last heating. There was still considerable glycogen in its liver. The gastric mucosa was hyperplastic. A papillary carcinoma of the breast showed no degenerated areas such as Schereschewsky found in his transplanted mouse carcinomas. Many megakaryocytes were present in the spleen.

Dog 44 was given the longest period of heating, nine intervals totaling thirty hours and twenty minutes. The rise of temperature was to 107.5 F. The animal was killed with chloroform one hour after the last heating. The pathologic changes did not differ strikingly from that of other dogs. Lymphoid germinal centers were very active. There was no increase in the liver fat. The kidneys were rather hydropic. The testis showed good spermatogenesis. There was arachnoid hemorrhage over the cerebrum. The bone-marrow was hyperactive. Ganglion cells about the adrenals showed vacuolar nuclear changes and migration of chromidial substance to the periphery.

The one outstanding feature of these three series of dogs which were given from one to nine heatings between the plates of the oscillator is the similarity of the tissue changes qualitatively and apparently quantitatively. The hyperthermia produced was about the same in all animals, although one degree of difference might have been of great importance to the animal in ways not clearly indicated. It seemed to make little difference whether the dog was being heated for the first or the ninth time. So long as he died during the heating or before his temperature had dropped more than a few degrees, the effects observed varied but little among the twenty-four dogs studied. These animals were of many breeds and sizes, both long-haired and short-haired varieties being represented.

It has been determined by Knudson and Schaible [1] that a dog subjected to this form of irradiation will show a gradual drop to a normal temperature in three hours. There was no tendency toward the development of a persistent hyperthermia following multiple heatings, although individual variation was noted among the animals as to their ability to endure such high temperatures. Evidence of increased cell activity was most evident in the parenchymatous organs, occasionally taking the form of so-called cloudy swelling with or without increase in the rate of cell division as indicated by the number of mitotic figures. Dehydration, which was quite evident in the high viscosity of the blood, was reflected also in the tissues. Breaking down of cells was most evident in the liver where various degrees of fatty degeneration and necrosis were produced and in the lymphoid structures which showed degenerative and necrotic changes.

Twenty-seven adult white rats were subjected to the same form of high frequency heating as the series of dogs. Eighteen animals were heated once, the time of exposure in the field fifty minutes to six hours and fifty-four minutes. The normal preheating temperatures varied from 98.2 to 101.8 F. The degree of fever obtained was from 103 to 112 F. The loss of weight was from 2 to 32 Gm., or from 2.1 per cent to as high as 11.2 per cent of body weight. There appeared to be no direct relation between the duration of the heating and the degree of fever, the maximum rise being obtained in a few minutes with subsequent heating affecting it little, if at all. There was a more definite relation of duration of exposure to the loss of weight, but exceptions to this were frequently encountered. In other words, there appeared to be much difference in susceptibility to heat between individual rats just as there is among man and other animals.

During the experiment the extremities of the rat would usually become hyperemic, the nose would "run," the mouth salivate, the anal mucosa would swell and the tail expand. In some rats, the tail would sizzle and literally explode, the skin of the entire length of the tail being disrupted (fig. 2). Gangrene of the tail would later develop, usually of the dry type.

Most of the rats were killed by a blow on the head, others with chloroform. The histologic changes in the organs were similar to those in the dogs. Hyperemia, dehydration, cloudy swelling, fatty and hydropic changes and focal hemorrhages were widespread. The lymphoid tissue showed much stimulation, and with longer continued heating, necrosis of the germinal centers. A normal gastrointestinal tract was rarely seen. Nematodes were often encountered. Postmortem changes set in early, but occasionally necrosis in the crypts of the gastric and intestinal glands with leukocytic reaction was found.

The kidneys, liver and heart usually showed marked fatty degeneration. In the liver, the change usually began in the peripheral zone of the lobule. Hemorrhages were frequently found in the adrenal cortex and peri-adrenal fat.

The ovaries appeared normal except for hyperemia. The testes, however, showed marked edema, congestion, occasionally degenerative changes in spermatogonia and spermatids, with proliferation of the Sertoli cells and the formation of giant cells free in the lumen of the tubules. The thyroid and parathyroids showed no lesions.

The brain was examined in several animals killed with chloroform. Hyperemia, edema, subpial hemorrhages and scattered intracortical hemorrhages were rather constant and also chromatolysis in cells of the pyramidal layer.

Glycogen depletion of the liver was moderate in rats heated for short periods and complete after four hours of heating. There was depletion of muscle and renal glycogen also. The bone-marrow was hyperactive in all rats.

Rats 2379, 2380, 2381 and 2382, all males, were heated daily over a period of three months. These animals when killed showed little abnormal. No fatty changes were found. Hyperemia and foci of atelectasis were present in the lungs. There was exhaustion or marked retardation of the spermatogenesis, with exfoliation of the germinal epithelium and proliferation of the Sertoli cells.

Five rats were heated in two or three periods for a total of from three to nine and one-fourth hours. Two developed "snuffles," but showed no bronchial

Fig. 2.—The tail of a rat given one heating of about ten minutes, with rapid rise of temperature. Acute congestion, thrombosis and melting of subcutaneous fat led to rupture of the skin at base of the tail and for much of its length, later followed often by dry gangrene. This injury to the tail is most pronounced when the animal is placed at right angles to the electrode plates during the heating.

or pulmonary changes except congestion. The rest of the organs showed approximately the same conditions as the rats heated but once for periods over two hours.

Three guinea-pigs responded similarly to the rats, a rise of temperature of 8 degrees in one hour being obtained. The tissue changes were similar to those in rats and dogs.

COMMENT

In the foregoing paragraphs we have tried to describe the morphologic picture of the tissues in several types of experimental mammals as seen after the animals had developed a hyperthermia while in the field of a high frequency oscillator. A fair judgment of this mechanism must be based, however, not alone on this descriptive study but also on a comparison with the effects of heat induced by other methods studied with equal care.

Abundant data are available concerning the effects of dry and moist heat externally applied. Diathermy and infra red rays have also been used considerably in recent years. The pyrexia of fever of central

origin would appear to be uncomplicated by infection and hence of value for comparison. The fever of infectious origin, however, includes accessory states such as bacterial toxemia, making a critical analysis of the febrile portion of such disease attended with great difficulty. Nevertheless, since 1917, when von Jauregg introduced malaria into the therapy of paresis, and typhoid vaccine had been used to induce a febrile reaction in the treatment of chronic arthritis, more attention has been given the rôle of fever in clinical medicine. Antipyretic drugs are no longer used as such, being relegated to limbo with "feed a cold and starve a fever" and other obsolete dicta.

Should the reader wish to center his ideas on fever about some one discussion of the subject, he is advised to use the Cartwright lectures on the pathology of fever by Prof. William H. Welch,[2] written in 1888. He reviews the subject thoroughly up to that time and also anticipates most everything that has been experimentally or clinically proved since then.

In his lecture on "The Nature of Fever," Dr. Welch recorded many observations which are worthy of emphasis here. In abstract, he said that fever is an abnormal elevation of temperature. Animals in fever lose weight more rapidly than healthy animals in hunger. There is an enormous increase in the excretion of urea in fever. It is difficult to produce experimentally in animals anything approaching in intensity the well marked fevers of human beings. No definite relation exists between heat production and the height of the temperature. A person usually produces far less heat in fever than he often does under circumstances which normally increase heat production, such as cool environment and muscular exercise. It is impossible to explain fever simply on the basis of excessive thermogenesis. Equilibrium is so disturbed that heat loss does not correspond with heat production. Most animal heat is produced by the muscles.

Concerning "the Effects of Increased Temperature of the Body," Welch stated that high temperature was coming to be regarded as a beneficent provision, vis medicatrix naturae, an opinion due in great part to the disappointment over the results of antipyretic drugs. There was no agreement of opinion as to what symptoms were due to high temperature and those due to infection, the high temperature being an index of the severity of the disease rather than a source of danger itself. In hyperpyrexia there is probably complete paralysis of heat regulation, and an analogous condition with similar dangers sometimes develops in animals artificially heated. It is evidently irrelevant whether the source of heat is within or without the body. A mammal artificially heated to

2. Welch, William Henry: The General Pathology of Fever, Cartwright Lectures, M. News **52**:365; 393; 539; 565, 1888.

111 or 113 F. develops convulsions and dies, and rigor mortis occurs promptly. Irritability of the heart muscle ceases, death being due to paralysis of the heart. Naunyn, he quotes, kept a rabbit alive thirteen days with an average temperature of 106.7 F. Welch kept rabbits in a box at 107.3 and 106.6 F. three weeks; both lost weight and one when killed showed fatty degeneration of the heart, liver and kidneys. Black and gray rabbits were more resistant to heat than white rabbits. The condition produced by artificial heating, he said, is not directly comparable with fever since in artificial heating loss of heat is reduced to a minimum, the external temperature being higher than the internal. Heat may be abnormally distributed in the body. In fever, infection may lower the tolerance to high temperature. The results of experiments in heat dyspnea in animals cannot be transferred directly to man because in animals respiration has a far more important influence on temperature regulation than in man—a dog pants, a human sweats. Welch noted that the liver first showed fatty degeneration, and then the heart and kidneys. Iwaschkewitsch, Legg and Litten found parenchymatous degeneration in the heart, liver and kidneys.

The forced inactivity of the muscles and imperfect ventilation may have played a part in the experiments. Infection greatly increased the fatty degeneration. The symptoms usually considered those of heart failure are often present in fevers with no visible degeneration in the heart muscle, and vice versa, but often they are associated. Loss of weight is due to increased consumption of tissues and also loss of water. The constipation of fever was explained as being due to the heated blood stimulating the nerves inhibiting peristalsis. There is a general law that within certain limits cell activity is more energetic at high than at low temperatures. Welch emphasized the great necessity of controlling the experimental method by clinical observation.

In the thirty years following the Cartwright lectures, fever came to be regarded more and more as a therapeutic force as is evident from the use of injections of foreign protein in the treatment of chronic arthritis and later by the employment of malarial fever in diseases of the central nervous system.

The structural alterations in the tissues as seen in our experiments with the high frequency oscillator can best be understood if the pathologic physiology is appreciated. Pemberton [3] summarizes the effects of external heat as follows: (*a*) heightened blood flow; (*b*) increased metabolism; (*c*) elimination of acids, carbon dioxide; (*d*) alkalosis; (*e*) tetany, which may result from the alkalosis, and (*f*) increase in lactic acid in the sweat. In the pathology of major heat stroke, there

3. Pemberton, R.: A Summary of the Effects of External Heat Upon the Human Body, Am. J. M. Sc. **169**:485, 1925.

are: (*a*) azotemia, due to renal injury; (*b*) spasm of the left side of the heart; (*c*) venous congestion; (*d*) contractions of the intestine and bladder; (*e*) dilatation of the stomach; (*f*) cloudy swelling of parenchymatous organs; (*g*) degeneration of the nerve cells; (*h*) edema of the lungs; (*i*) no connective tissue changes, and (*j*) no ketone acidosis but lactic acidosis.

Hot baths, while from time immemorial a popular panacea, have been given more careful study in recent years and their therapeutic scope widened. Mehrtens and Poupirt [4] noted the effects of hyperpyrexia produced by hot baths on diseases of the central nervous system such as paresis, combined sclerosis, tabes, encephalitis and others. Definite clinical improvement was obtained in many cases. The permeability of the meninges was increased when the temperature was above 103 F. and the colloidal gold curve of paretic patients changed to a tabetic curve. The Wassermann reaction of the spinal fluid was frequently diminished. The blood picture tended to show increased hemoglobin and red cell counts and increased reticulocytes.

Von Kennel [5] found that the normal vesiculation time with cantharides plaster is reduced during the height of fever. He regards the increased permeability of the cells of the body an important factor in the action of modern fever therapy.

In recent years, diathermy has come to occupy a prominent place in physiotherapy and the effects of the heat produced by its relatively low rate of alternating current have been widely studied. King and Cocke,[6] using a variofrequency diathermy machine at 3,500 milliamperes found that the temperature rises slowly during the first thirty minutes, and then more rapidly to 104.5 F. and falls slowly in from six to seven hours to normal. No changes in the blood chemistry were found in several cases so heated. Eight of twenty cases of paresis were improved, and the colloidal gold curve favorably altered. One patient developed acute nephritis at the end of eight treatments, but that the heating was the cause of this is not conclusively shown.

The physiologic effects of currents of very high frequency (from 135,000,000 to 8,000,000 cycles per second) were studied by

4. Mehrtens, H. G., and Poupirt, P. S.: Hyperpyrexia Produced by Baths: Its Effect on Certain Diseases of the Nervous System, Arch. Neurol. & Psychiat. **22**:700, 1929.

5. von Kennel, J.: Die Permeabilität der Meningen, insbesondere bei der modernen Fiebertherapie, Deutsches Arch. f. klin. Med. **165**:180, 1929.

6. King, J. C., and Cocke, E. W.: Therapeutic Fever Produced by Diathermy, with Special Reference to Its Application in the Treatment of Paresis, South. M. J. **23**:122, 1930.

Schereschewsky [7] in 1926. He noted that when small laboratory animals were placed in a box of insulating material and subjected to the action of such a current, severe symptoms were caused which resulted in death when the exposure was prolonged. Part at least of the symptoms were thought due to heat retention. The sequence of events with the exposed animals was as follows: At first, the mouse was quiescent, then agitation began which increased with the length of exposure. The ears, tail and paws turned bright pink, and often became livid or cyanotic as the exposure was prolonged. There were salivation and increased nasal secretion. The head, under parts and paws became moist. After a variable time, convulsions and convulsive winking set in with dyspnea. Finally, respiration ceased. The body of the mouse was warm to the touch, and its rectal temperature varied from 42.2 to 44 C. (normal from 37 to 39 C.).

Death often occurred with a moderate temperature (39.2 C.). The primary fatal effect was considered due to the increased body temperature. A mouse killed with carbon monoxide and heated at once with a lethal dose showed little or no rise in temperature, suggesting a heating effect different from diathermy. With the high frequency current in a diathermy apparatus, it is easy to raise the temperature of dead tissues well above the point at which albumin coagulates.

Among the sequelae were small hemorrhagic areas along the course of the blood vessels of the ears. In forty-eight hours, the ears became necrotic and fell away. The tail showed ecchymoses, with later gangrene and dropping off. Alopecia of the supra-orbital regions and panophthalmitis sometimes developed.

The effects observed were most marked in a band of frequencies extending from $F = 66 \times 10^6$ cycles to $F = 18.3 \times 10^6$ cycles. Schereschewsky was of the opinion then that, under the conditions of the experiments, there was a differential action with respect to frequency, the lethality of a constant current being in one region of the spectrum inversely, and in another directly proportional to frequency. He stated "since frequency is the sole differentiating characteristic in the whole band of radiant energy it is perhaps to be expected to find that in electromagnetic waves frequency is a determining factor in their mode of action on living organisms."

Schereschewsky [8] also studied the action of currents of very high frequency on a transplantable mouse carcinoma (Crocker Research

7. Schereschewsky, J. W.: The Physiological Effects of Currents of Very High Frequency (135,000,000-8,300,000 Cycles per Second), Pub. Health Rep. **41**: 1939, 1926.

8. Schereschewsky, J. W.: The Action of Currents of Very High Frequency upon Tissue Cells: (a) Upon a Transplantable Mouse Carcinoma, Pub. Health Rep. **43**:16, 1928.

Lab. No. 180), a tumor which gave 96 per cent of "takes" and only 2 per cent spontaneous recessions. The limits used were from 66,000,000 to 68,000,000 cycles per second, from 200 to 500 milliamperes. The tumors were implanted at McBurney's point, and after a certain amount of growth were pinched between the insulated plates of treatment electrodes. When insulation of the plates was faulty, burns were produced. Softening of the tumors followed exposure in the field. One hundred of 403 mice survived free from tumor. No spontaneous recessions occurred in 230 control mice. The skin showed edema and depilation. The action of the high frequency currents seemed to Schereschewsky not the same as in diathermy, since with 300 milliamperes and only from three to four minutes exposure there was no significant local heating.

Prof. S. B. Wolbach examined the tumor tissues after their treatment and reported that there was "necrosis of tissue cells and accompanying vascular and connective tissue structures, a coagulative necrosis-like infarction. Extraordinarily rapid disappearance of the tumor. I am quite unfamiliar with anything corresponding to it. Autolysis?" The treatment of the mice appeared to decrease their resistance to infection.

The author mentioned a hypothesis of Prof. G. W. Pierce: "Tissue cells placed in an electrostatic field and subject to the displacement currents caused by the rapid alternations in polarity of the field may undergo some electromechanical vibration which might have definite effects upon the cells."

Kahler, Chalkley and Voegtlin [9] observed the effect of a high frequency electric field on *Paramecium caudatum,* using 10,000,000 cycles. The temperature of the medium was 30 C. At 41 C., all motility was lost, the organisms became opaque and many disintegrated. No recovery was noted after opacity occurred. No demonstrable effect was seen under sublethal heating either by high frequency or the direct method. There was an identical appearance of the organisms when killed by either way. The chief effect was that of heating, due to the rapidly changing electrostatic field.

Carpenter and Boak [10] found that rabbits inoculated intratesticularly with *Spirochaeta pallida* and heated in the same machine as was used in many of our experiments, four, five and seven days after inoculation either failed to develop the primary lesion or showed very slight evi-

9. Kahler, H.; Chalkley, H. W., and Voegtlin, C.: The Nature of the Effect of a High Frequency Electric Field Upon Paramoecium Caudatum, Pub. Health Rep. **44**:7, 1929.

10. Carpenter, C. M., and Boak, R. A.: The Effect of Heat Produced by an Ultra High Frequency Oscillator on Experimental Syphilis in Rabbits, Am. J. Syph. **14**:346, 1930.

dence of infection. They were of the opinion that the effect on the spirochete is due largely to the heat that is produced within the body.

MacCreight and McKinley [11] exposed albino rats in an electrostatic field of 100,000,000 cycles frequency, their study being undertaken because "there is at present a premature trend toward the use of the vacuum tube high frequency generator in therapeutics." They found that death of the animals was accompanied by a violent rush of blood to the fore and hind limbs and tail, which became severely congested and swollen. A comparison was made with the effects of external heat in a dry oven at temperatures of 45, 55 and 65 C., the animals so killed showing no discernible rush of blood to the limbs or tail. It was only when temperatures reaching 160 were used that the effects of external heat were fairly comparable with those obtained in electrostatic fields.

Mellon, Szmanowski and Hicks [12] reported an effect of short electric waves on diphtheria toxin which they regard as independent of the heat factor. A temperature of from 38 to 40 C. in a water bath with alternate chillings and heatings did not affect the toxin of the control sample, but the radiated sample was definitely attenuated in as short a time as fifteen minutes. They suggest that the irradiated diphtheria toxin be investigated with regard to its properties as an immunizing substance.

The question is naturally asked: "Are the morphological or chemical changes in the tissues exposed in a high frequency electrostatic field due to some factor other than heat?" The chemical studies of Knudson and Schaible [1] contain no suggestion of such an influence. Our histologic studies in the dog, white rat and guinea-pig as a whole reveal the usual picture of hyperthermia described as long ago as 1888 by Welch, namely, fatty degeneration of parenchymatous organs, dehydration of tissues, congestion of the organs and focal hemorrhages. Cloudy swelling was probably more marked in our animals than is usually the case with external applications of heat. The degree of congestion obtaining in the appendages leading to thrombosis and gangrene of the tail, ears and feet was a quantitative difference to be carefully considered in the heating of human beings. The acidosis and glycogen depletion also are natural results of intracellular hyperthermia. Other changes such as lymphoid degeneration and necrosis are of the same significance.

The work of Mellon, Szmanowski and Hicks [12] on diphtheria toxin suggests an effect other than that of heat. Their experiments are not

11. MacCreight, J., and McKinley, G. M.: The Biological Effects of Temperature Variations with High Frequency Oscillations, Proc. Soc. Exper. Biol. & Med. **27**:841, 1930.

12. Mellon, R.; Szmanowski, W. T., and Hicks, R. A.: An Effect of Short Electric Waves on Diphtheria Toxin Independent of the Heat Factor, Science **72**:174, 1930.

exactly comparable with those performed on living cells but nevertheless constitute probably the only evidence so far available of a nonthermal alteration of an organic substance in the field of the oscillator.

The ease with which high frequency heating produces congestion of the extremities suggests that it may be of value when cautiously used, in the treatment of certain forms of peripheral ischemia, such as occurs in Raynaud's disease, Buerger's disease and arteriosclerosis.

The morphologic changes in the experimental animal so far as our studies go reveal no lesions which cannot be anticipated in the method of using the high frequency oscillator. The dangers are rather obvious, but once understood, experimentation with human disease under proper supervision would seem justifiable. Such work is in progress in the department of medicine of Albany Medical College, under the direction of Dr. Thomas Ordway, and also in other institutions. The results of these lines of investigation should be of great interest.

It cannot be too strongly emphasized that the utmost care be shown in evaluating postmortem changes in animals that have died in hyperthermia. Autolytic changes occur very rapidly. In all experimental studies with heat, the interval before fixation of the tissues should be noted and stated in the reports. The alterations in experimental mouse cancer described by Wolbach in Schereschewsky's [8] series suggested acute autolytic processes. In one of our dogs, a papillary carcinoma of the breast was apparently unaffected after five heatings totaling nineteen and one-half hours, a much longer exposure than was necessary to produce definite softening of the experimental mouse tumors.

Another possible danger is the effect of high frequency currents on germinal cells. In the male animals with their testes more or less externally situated, degenerative changes were sometimes produced. It is well known that the male germ cells are very susceptible to heat.

A generalized increase in the metabolic rate of the tissue cells is evident in the parenchymatous organs and also in the bone-marrow which was invariably hyperactive. Whether this fact warrants the use of high frequency electric waves in anemia or leukopenia, remains to be proved.

SUMMARY

A study was made of the effects on animal tissues of exposure in the electrostatic field of a high frequency oscillator. Twenty-three dogs, twenty-seven adult white rats and three guinea-pigs were used in the experiment.

A marked hyperthermia was produced in the animals, the amount of temperature increase being controllable by altering either the voltage or the distance between the plate electrodes of the apparatus.

The morphologic changes occurring in the tissues were congestion of the organs, peripheral hyperemia, cloudy swelling, fatty degeneration,

dehydration, glycogen depletion, focal hemorrhages, especially in the gastro-intestinal tract, epithelial hyperplasia in the parenchymatous organs and stimulation of the bone-marrow. Following prolonged periods of heating, degenerative lesions occurred in the male germinal epithelium.

From a morphologic point of view the alterations observed differ but little from the effects of fever produced by various other methods, but the ease with which the temperature can be controlled in the high frequency field of this apparatus and the character of some of the tissue responses suggest possible therapeutic applications.

HYPERTENSION IN RELATION TO THE BLOOD VESSELS OF THE MEDULLA OBLONGATA*

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Bordley and Baker [1] in 1926 formulated the theory that hypertension was due to arteriosclerosis of the blood vessels of the medulla oblongata. The basis of this theory was formed on the experiments of Anrep and Starling,[2] who found that a decreased blood supply to the brain causes an excitation of the vasomotor center, which results in a systemic increase of blood pressure. Bordley and Baker believed the location of the vasomotor center to be in the region of the obex. The reason for this conception was an investigation of Ranson and Billingsley,[3] who showed, in the cat, that stimulation of the floor of the fourth ventricle seemed to locate the vasodepressor center lateral to the obex and the vasopressor center at the ala cinerea. Because of these experimental observations, Bordley and Baker studied the blood vessels of the medulla oblongata in the region of the obex. In their series, they found that in all the cases of prolonged hypertension there was arteriosclerosis of the blood vessels of the medulla oblongata, whereas in cases with normal blood pressure no arteriosclerosis of the vessels of this region was present. Cutler [4] in 1928 was unable to substantiate the claims of Bordley and Baker. He found that in some cases of hypertension arteriosclerosis of the vessels of the medulla oblongata was not shown. He studied alsc the vessels that supply the medulla, but he could not find that in arteriosclerosis there were sufficient anatomic changes of the vessels to suggest a relationship to hypertension.

In the present study the blood vessels of the medulla oblongata in the region of the obex were examined in twenty-four cases of hypertension and in thirty-five cases in which the blood pressure was normal. The

* Submitted for publication, Oct. 10, 1930.

* From the Pathological Institute of the University and the German Research Institute for Psychiatry (Kaiser Wilhelm Institute), Munich, and the Pathological Laboratory of the Buffalo General Hospital.

1. Bordley, J., III, and Baker, B. M., Jr.: Bull. Johns Hopkins Hosp. **39:** 229, 1926.

2. Anrep, G. V., and Starling, E. H.: Proc. Roy. Soc., London, s. B. **97:**463, 1925.

3. Ranson and Billingsley: Am. J. Physiol. **41:**85, 1916.

4. Cutler, O. I.: Relation of Arteriosclerosis of the Cerebral Vessels to Hypertension: Distribution of Arteries Supplying Pons and Medulla, Arch. Path. **5:**365, 1928.

cases of hypertension that were chosen occurred chiefly in older persons in whom the hypertension was of some duration. In order to compare the vessels in cases of hypertension with the vessels in patients with normal pressure, the medulla oblongata was studied in persons varying in age from 20 to 85 years.

In this report, arteriosclerosis is considered to be of three types. The first of these is arteriosclerosis of the large vessels which is regarded as a connective tissue and elastic fiber hyperplasia of the intima with retrogressive changes. This is arteriosclerosis in the narrow sense, but in the broad sense two other types are included. The second is senile angiectasis, which is a laying down of connective tissue in all the walls of the blood vessels. The third is arteriosclerosis of the arterioles, which is considered to be a hyaline change taking place under the endothelium. Jakob,[5] however, believed that this hyaline change of the arterioles of the central nervous system is found not only in arteriosclerosis, but in pellagra, syphilis, chronic intoxication and senility. Aside from the arteriosclerotic changes of the vessels, a reduplication of the elastic fibers was found in the endothelium in a few vessels. Such a reduplication was regarded by Jakob as an indication of syphilis, but since syphilis could not be demonstrated, the change was considered physiologic, owing to advancing age. Sections of the medulla oblongata were taken from the region of the obex. Frozen, paraffin and colloidin preparations were made and stained by the usual methods for the study of blood vessels.

OBSERVATIONS IN CASES OF HYPERTENSION

This group was composed of twenty-four cases, in twelve of which arteriosclerosis of more than one vessel of the medulla oblongata was shown. The arterioles in the region of the olives and the larger vessels in the center of the medulla were chiefly affected. According to Cutler,[4] the vessels in the vicinity of the olives are short and terminate near their entrance along the lateral surface of the medulla, so that it would seem that vascular lesions in the olives would not affect the vasomotor center, since its location is believed to be in the floor of the fourth ventricle.

Of the other twelve cases of hypertension, five showed hyaline change in only one arteriole of the medulla. The important points in one of these cases were as follows:

The patient was a woman, aged 58. Two years before death, she was reported to have an enlarged heart with a systolic murmur at the cardiac apex. The blood

5. Jakob, A.: Das Grosshirn, Vienna, Franz Deuticke, 1927.

pressure at this time was recorded as 220 systolic and 110 diastolic. In the next two years the blood pressure varied from 219 systolic and 110 diastolic to 180 systolic and 95 diastolic. Death occurred from myocardial insufficiency. At autopsy marked hypertrophy of the heart and granular atrophic kidneys were found. Microscopic sections of the kidneys showed arteriosclerosis of the arterioles and larger vessels. In the medulla oblongata, one arteriole with a thick layer of hyaline beneath the endothelium was found near the olive.

Arteriosclerotic changes in the vessels of the medulla oblongata were not found in the seven remaining cases of hypertension. Of these, three occurred in men who died from uremia. They varied in age from 31 to 42, and had entered the hospital because of symptoms due to hypertension and chronic nephritis. The arterioles of the medulla oblongata showed only a thickened elastic layer. A fourth case in this group of seven was that of a man of 84 years, whose blood pressure a short time before death from coronary thrombosis was 190 systolic and 110 diastolic. One year previously the blood pressure had been 190 systolic and 90 diastolic. Autopsy revealed an enlarged heart and granular atrophic kidneys, the microscopic sections of which showed arteriosclerotic changes. The media in a few vessels of the medulla was slightly thickened.

Three other patients with hypertension without arteriosclerosis of the vessels of the medulla oblongata died from apoplexy. One was a man aged 71, with mild general arteriosclerosis; another was a man aged 39, with essential hypertension; while a third was a man aged 45, who was known to have had hypertension and an enlarged heart for eight months.

This patient entered the hospital with symptoms simulating tumor of the brain. The blood pressure was 200 systolic and 100 diastolic. Albumin and casts were found in the urine. Ophthalmoscopic examination showed retinitis. Death occurred suddenly after the patient had been a few days in the hospital. At autopsy a fresh hemorrhage at the base of the brain, granular atrophic kidneys and hypertrophy of the heart were found. Arteriosclerosis of the blood vessels of the medulla oblongata was not demonstrable, yet marked arteriosclerotic changes were present in the blood vessels of the kidneys.

OBSERVATIONS IN CASES IN WHICH THE BLOOD PRESSURE WAS NORMAL

Among the thirty-five cases in which the blood pressure was normal, six were found in which one or more blood vessels of the medulla oblongata showed hyaline change. Enlargement of the heart was not present in these cases, but mild arteriosclerosis of the aorta and of the peripheral vessels was found, as well as arteriosclerotic changes in the kidneys, except in case 5, in which there was pyelitis.

Case 1 of this group was that of a woman of 61 years, committed to the hospital because of a psychosis and arteriosclerosis. The blood pressure readings during her few months in the hospital varied from 165 systolic and 70 diastolic to 160 systolic and 70 diastolic. At autopsy generalized arteriosclerosis and atrophy of all organs were found. One large blood vessel with a hyaline change and several smaller ones were present in the medulla oblongata.

Case 2 was that of a man, aged 77. He had been a patient in the hospital for several months because of carcinoma of the stomach. The urine showed a trace of albumin. The three recorded blood pressure readings were approximately 145 systolic and 85 diastolic. In one arteriole in the medulla a proliferation of the endothelium was found, but many showed hyaline change.

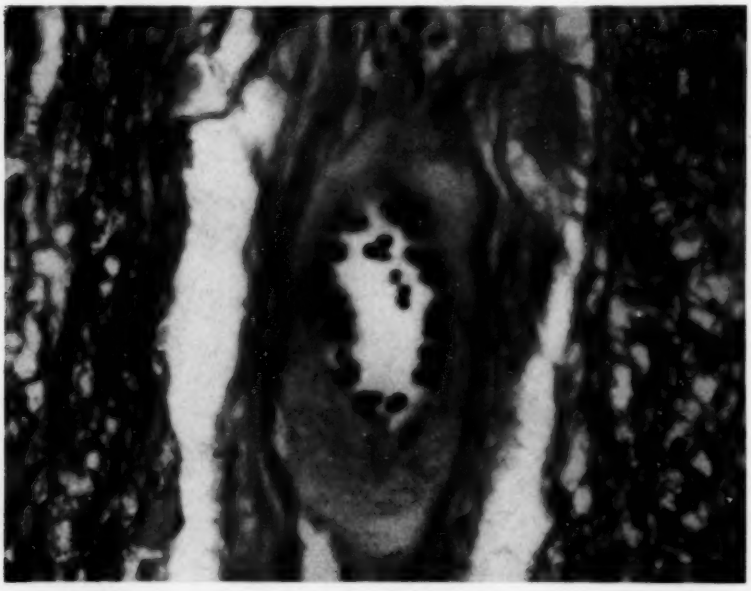

Fig. 1.—Hyaline change beneath the endothelium of a blood vessel in the medulla oblongata of a woman, aged 61, whose blood pressure was 165 systolic and 70 diastolic. Van Gieson's stain was used; × 500.

Case 3 was that of a woman, aged 65, who remained in the hospital for one year with arteriosclerosis and empyema of the lungs. The blood pressure, taken at frequent intervals, showed an average reading of 100 systolic and 65 diastolic. The arterioles in the medulla were either partially or completely hyalinized beneath the endothelium.

Case 4 occurred in a man, aged 73, who had been in the hospital for many years with involution melancholia. Physical examinations made during that time yielded essentially negative results. The blood pressure readings for the last three years were: 155 systolic and 85 diastolic, 130 systolic and 75 diastolic and 120 systolic and 75 diastolic. Shortly before death from a rapidly growing carcinoma of the bladder, the blood pressure was 150 systolic and 60 diastolic. One arteriole in the medulla showed complete hyaline change beneath the endothelium while in many others partial hyaline degeneration was observed.

Case 5 was that of a man of 41 years, who entered the hospital because of diabetes. The blood pressure during several months varied from 125 systolic and 75 diastolic to 110 systolic and 65 diastolic. Death occurred from an ascending infection of the urinary tract. Several arterioles in the medulla oblongata were completely hyalinized beneath the endothelium.

Case 6 was that of a woman, aged 69, who had been in the hospital for many years with a schizophrenic reaction. The blood pressure readings of this patient at the yearly examination for four years previous to death were: 110 systolic and 72 diastolic, 128 systolic and 72 diastolic, 140 systolic and 70 diastolic and 134 systolic and 66 diastolic. The patient appeared apparently healthy until difficulty

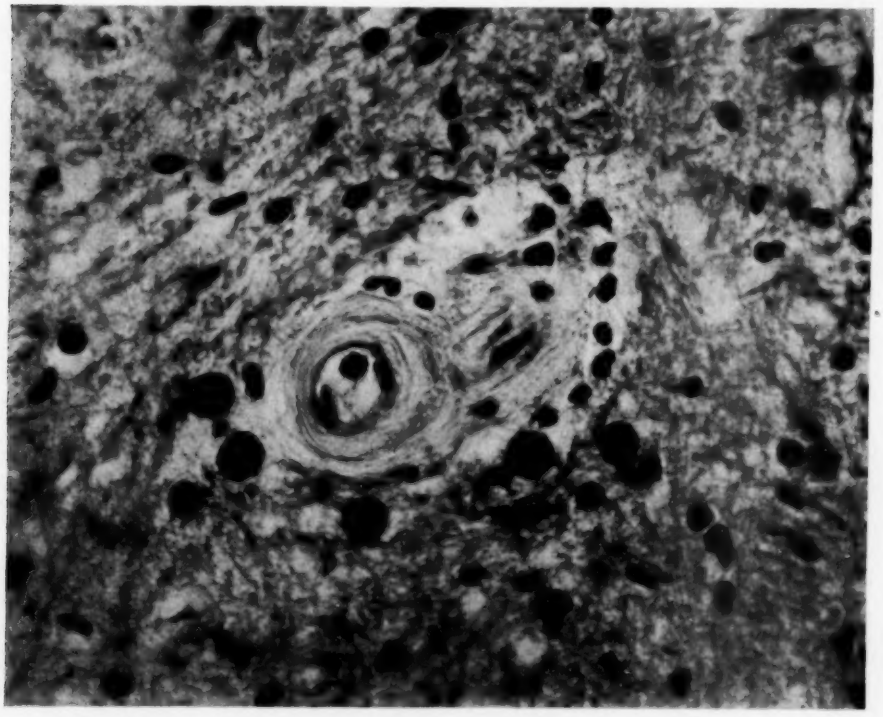

Fig. 2.—Blood vessel of the medulla oblongata, showing hyaline change beneath the endothelium, in a man, aged 69, whose blood pressure was 142 systolic and 70 diastolic. Hematoxylin and eosin stain was used; × 500.

in swallowing developed. Carcinoma of the esophagus was found from which she died in a few months. Three arterioles in the medulla oblongata showed a thick layer of hyaline beneath the endothelium.

Sections of the brain were also examined in this series of fifty-nine cases, but no case was found in which the only vessels showing arteriosclerosis were those of the medulla oblongata, although such an observation would be necessary to prove the theory of Bordley and Baker.

CONCLUSION

The blood vessels of the region of the obex of the medulla oblongata were studied in twenty-four cases of hypertension of varying duration and in thirty-five cases of normal blood pressure. In twelve cases of hypertension, arteriosclerosis of the vessels of the medulla oblongata was found, but in the other twelve cases slight or no arteriosclerosis of these vessels was present. Among the cases of normal blood pressure, six showed arteriosclerosis of the vessels of the medulla oblongata. However, in none of the cases was arteriosclerosis confined solely to the vessels of the medulla oblongata. Therefore, in this histologic study of the vessels of this region no proof is found that hypertension is the result of arteriosclerosis of the vessels of the medulla oblongata.

THE RATE AND LOCATION OF REMOVAL OF BACTERIA FROM THE BLOOD IN HUMAN DISEASE*

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Numerous experimental observations on animals have shown that bacteria which gain entrance to the blood stream are removed from it with great rapidity.

Wysokowitsch,[1] in his classic studies in 1886, injected large numbers of all sorts of bacteria into the blood of rabbits and dogs and showed that both pathogenic and nonpathogenic organisms disappear completely from the blood in a variable time—from seven minutes to three or four hours. Organisms pathogenic for the experimental animal then reappear after some hours and progressively increase in numbers. He carefully proved that there was no excretion of the bacteria by the kidneys or gastro-intestinal tract. In animals killed or dying after from one to several days he showed that many of the bacteria were still alive, and that they were concentrated in certain organs—chiefly the liver, spleen and bone marrow (he did not examine the lungs). He was able to demonstrate bacteria in the endothelial cells of the capillaries of the liver and of the splenic pulp.

Werigo,[2] in 1894, injected anthrax bacilli into rabbits, and after a few minutes found that they had accumulated in great numbers in the lungs, where they were mainly engulfed in polymorphonuclear cells in the capillaries. There were many in the liver and the spleen.

Weil [3] found that virulent streptococci injected into the blood stream of guinea-pigs are gradually removed by the filtering effect of the tissues. The blood had practically no bactericidal effect. Thus after intravenous injection of bacteria into guinea-pigs the blood showed the following numbers of colonies of bacteria per cubic centimeter at five minutes and at one and a half hours, respectively: 4,000 and 192 in one case; 16,000 and 84 in a second; 4,000 and 612 in a third, and 3,000 and 544 in a fourth. In most cases there was subsequent increase of the number of organisms and death of the animal.

* Submitted for publication, Oct. 13, 1930.
* From the Laboratories of Mount Sinai Hospital.

1. Wysokowitsch: Ztschr. f. Hyg. u. Infektionskr. **11**:3, 1886.
2. Werigo: Ann. de l'Inst. Pasteur **8**:1, 1894.
3. Weil: Ztschr. f. Hyg. **68**:346, 1911.

Bull,[4] in 1915, injected large doses of pneumococci into the blood stream of rabbits (for which these organisms are highly virulent). In those animals which received simultaneous injections of antipneumococcus serum in another vein, the blood was sterile fifteen minutes later, while in the animals which did not receive serum the blood showed about 1,000,000 organisms per cubic centimeter. (In the animals the blood of which was thus transiently sterilized, the organism reappeared in the blood about twelve hours and caused death.) Examination of the organs showed that clumped bacteria were taken up by phagocytes, chiefly white blood cells, but also by endothelial cells. The active white blood cells did not stay in the circulation (confirming an observation of Wysokowitsch,[1]) but accumulated in enormous numbers in the capillaries of the lungs, liver and spleen.

Bull attributed this effect to the agglutinative power of the serum and further confirmed this opinion by his work on typhoid and dysentery bacilli. The former are not pathogenic for the rabbit and are agglutinated by rabbit's serum. They are removed very rapidly from the rabbit's circulation. Thus, in one case typical of a number of experiments with typhoid bacilli, the numbers of colonies per cubic centimeter of blood were at one minute, 10,000,000; at two minutes, 2,500,000; at five minutes, 100,000; at fifteen minutes, 40, and at twenty minutes, 1.

Hopkins and Parker,[5] in 1918, injected hemolytic streptococci into cats and rabbits. Immediately after injection in cats the bacteria were more numerous in a given weight of lung than in the same weight of liver or spleen, while in rabbits they were more numerous in liver and spleen. (The same curious difference between cats and rabbits was found by Drinker and Shaw [6] with manganese dioxide particles injected into the blood stream. They also showed that the particles primarily held in the lungs were, in about eighteen hours, transferred to the liver.)

Manwaring and Coe [7] offered an explanation of the sudden removal of bacteria from the blood, at least in immune animals. They perfused surviving livers (previously washed free of blood), with pneumococci suspended in Ringer's solution or in normal serum. They found that the organisms came through in practically unchanged numbers unless immune serum was added. As small a concentration of immune serum as 1 : 1,000 caused complete retention of the bacteria by the liver. The opsonic power of the serum can evidently cause bacteria to be taken up by the fixed reticulo-endothelial cells of the liver, as well as by leuko-

4. Bull: J. Exper. Med. **22**:457, 475 and 484, 1915; **24**:25, 1916.
5. Hopkins and Parker: J. Exper. Med. **27**:1, 1918.
6. Drinker and Shaw: J. Exper. Med. **33**:77, 1921; **57**:8, 1929.
7. Manwaring and Coe: J. Immunol. **1**:401, 1916.

cytes. Manwaring and Coe found no such effect with lungs, kidneys, intestines or lower extremities of dogs.

There have been few direct observations on the removal of bacteria from the blood in human beings. The mechanism as discovered in other animals has been tacitly assumed to apply. Libman and Celler [8] saw as many as seventy-two organisms per cubic centimeter of blood disappear from the circulation within an hour after resection of the internal jugular vein and operation for sinus thrombosis. Schottmüller [9] stated that he had frequently seen large numbers of bacteria—as many as 1,000 per cubic centimeter of blood—in the circulation immediately after curettage for septic abortion, only to find the blood sterile fifteen minutes later. In spite of the enormous number of bacteria in the circulation, few cases of invasion of the blood stream ever show metastatic foci—about 2 per cent. Schottmüller stated that entrance of bacteria into the blood stream is of itself one of the most harmless of occurrences—far more innocuous than their entrance into cellular tissue or peritoneum.

In the present paper will be presented data (for the most part obtained for a different purpose) which further indicate that in human disease there is often a rapid filtration of bacteria from the blood.

Four years ago a technic was developed [10] by which blood could be withdrawn safely from the internal jugular veins. The object was to make simultaneous blood cultures from the two internal jugular veins in order to confirm the diagnosis of sinus thrombosis. A very great number of colonies per cubic centimeter of blood in the one jugular vein as compared with the other was regarded as diagnostic of lateral sinus disease. This procedure has now been carried out in fifty-seven cases. In thirty-five of the more recent cases a simultaneous blood culture was also made from a vein of the arm and the number of colonies counted there also; in some cases simultaneous cultures were also made from an artery; and in one instance in which diagnosis lay between osteomyelitis of the femur and acute bacterial endocarditis, the cultures were made simultaneously from the two femoral veins and from a vein of the arm. The results as bearing on sinus thrombosis are presented elsewhere.[11] The objects in the present paper are (1) to discuss the

8. Libman: J. Michigan M. Soc. **23**:462, 1924. Libman and Celler: Am. J. M. Sc. **138**:409, 1907.

9. Schottmüller: Verhandl. d. Gesellsch. f. inn. Med. **37**:150, 1925. Schottmüller and Binghold, in Mohr and Staehlin: Handbuch der innere Medicine, Berlin, Julius Springer, 1925 vol. 1, pt. 2, p. 786.

10. Ottenberg: Differential Jugular Blood Cultures in Sinus Thrombosis J. A. M. A. **90**:1602, 1928; Laryngoscope **37**:424, 1927.

11. Ottenberg: Differential Blood Cultures, J. A. M. A. **94**:1896, 1930.

meaning of the large difference which was found in some of the cases of sinus thrombosis between the number of colonies in the vein of the arm and those in one or both jugular veins, and (2) to study the results of the simultaneous cultures from artery and vein.

The cases were of two kinds, (1) those (all of otitic origin) in which the vein directly draining the affected area could be aspirated and the number of colonies per cubic centimeter of blood compared with that in other veins, and (2) control cases in which no vein directly draining the lesion could be aspirated, but in which several peripheral veins (and in some instances an artery) were simultaneously aspirated; the latter were chiefly cases of bacterial endocarditis. The cases of otitis are presented in table 1, the control cases in table 2.

TABLE 1.—*Blood Cultures in Cases of Sinus Thrombosis with Positive Simultaneous Plates from Vein of Arm and Both Jugular Veins*

Case	Diagnosis	Colonies of Streptococci per Cc. of Blood		
		Right Jugular Vein	Left Jugular Vein	Vein of Arm
57	Right sinus thrombosis	289	131	23
46	Right sinus phlebitis	165	64	88
41	Mastoiditis, right sinus phlebitis	1½	1	⅛ (femoral vein)
38	Left sinus thrombosis	1	45	27
34	Left sinus thrombosis	9	2	1
	(after operation)	21	..	5
32	Right sinus thrombosis	250	240	⅛
29	Left sinus phlebitis	34	89	9
25	Right sinus thrombosis	600	11	1
23	Mastoiditis plus exposure of right sinus (sinus phlebitis)	24	7	0
9	Cavernous sinus thrombosis	14	70	24
4	Left sinus thrombosis	122	7	6

OBSERVATIONS ON THE DISAPPEARANCE OF BACTERIA FROM THE BLOOD AND EXPLANATIONS

It will be seen on looking over table 1 that in every instance of lateral sinus infection the number of bacteria in the vein of the arm was smaller than in one or both jugular veins. In some instances this disproportion was great, as in case 25 with 600 colonies per cubic centimeter of blood in the right internal jugular vein and only 1 colony per cubic centimeter in the vein of the arm. On the other hand, in 5 cases of bacterial endocarditis the numbers of colonies in the vein of the arm and in the two internal jugular veins were approximately equal. In one case of acute bacterial endocarditis the numbers in the two femoral veins and the cubital vein were equal. And in two cases of sepsis from venous lesions on the trunk the numbers of colonies from the jugular veins and a vein of the arm were equal (table 2).

Two possible explanations might be offered for the small number of bacteria in the distant, as compared with the local, vein in most of

the cases of otitis. It might be due (1) to mere dilution of the jugular blood in the general blood volume or (2) to removal of bacteria at some place in the blood circuit.

The Possibilities of Dilution as an Explanation.—How rapidly would bacteria accumulate in the general circulation if they were being fed in at a steady concentration in the internal jugular vein?

This would obviously depend on (1) the volume and speed of the general circulation and (2) the ratio of the blood contributed by one jugular vein to the total venous return to the heart. The former data are well known. To get an approximate idea of the ratio of the jugular to the total venous blood I have measured the jugular veins and the superior vena cava of a cadaver. The circumferences of these veins

TABLE 2.—*Control Cases*

Case	Diagnosis and Organism	Colonies per Cc. of Blood		
		Right Jugular Vein	Left Jugular Vein	Vein of Arm
56	Subpectoral abscess, phlebitis of axillary vein; Streptococcus B	1	1	½
55	Cellulitis of perineum, phlebitis of right hypogastric vein, multiple embolic abscesses; Staph. aureus	3/8	2/8	4/8
52	Acute bacterial endocarditis (femoral culture to rule out osteomyelitis of femur); Streptococcus B	Right femoral vein, 500*	Left femoral vein, 500	500
39	Subacute bacterial endocarditis; Streptococcus A	153	175	200
35	Subacute bacterial endocarditis; Streptococcus A	11	3†	10
20	Acute bacterial endocarditis; Streptococcus B	258	...	282
15	Subacute bacterial endocarditis; Streptococcus A	14	10	16

* Numbers are only approximate, the colonies being too numerous for accurate count but apparently the same on all plates.

† Inaccurate; only one plate from left jugular.

were as follows: internal jugular vein, 16 mm.; superior vena cava, 48 mm., and inferior vena cava, 60 mm. From these circumferences the cross-sections of the full veins can be calculated: internal jugular vein, 25.2 sq. mm.; superior vena cava, 125.8 sq. mm., and inferior vena cava, 284 sq. mm. If it is assumed that the pressures in the three veins are nearly the same, the relative amounts of blood passing through them should be approximately in proportion to the areas of their cross-sections. The combined area of cross-sections of the superior and inferior vena cava is $126 + 284 = 410$ sq. mm. That of one jugular vein is 25.4 sq. mm. The ratio between the two $= \frac{25.2}{410} = \frac{1}{16.5}$ The amount of blood returned by one jugular vein in this person then was about one-sixteenth of the total blood returned to the heart in any interval of time.

In an adult whose total blood volume made one circuit per minute (a not impossible figure [12]) the amount of blood passing through the jugular vein in one minute would be one-sixteenth of the total volume. In sixteen minutes the amount of blood contributed by one jugular vein would equal the total blood volume. So that after sixteen minutes, if bacteria were contributed steadily by the jugular vein, the number of bacteria per cubic centimeter of blood in the general circulation should equal the number per cubic centimeter being contributed by the jugular vein, or the concentration in the rest of the blood at this time (if no bacteria were removed) should be one-half the concentration in the jugular vein (since the jugular vein would contain as many as the general circulation plus its new contribution of the moment).

Similarly at the end of a second period of sixteen minutes, the number of bacteria in the general circulation would be twice the number at that moment being contributed by the jugular vein, and so on; in each period of sixteen minutes the number in the general circulation would come closer to that in the jugular vein.[13]

If the time of the circulation of the blood were less than one minute (and it generally is, particularly when the pulse is rapid, as in fevers), the time needed for the concentration of bacteria in the general circulation to approach that in the jugular vein would be proportionately shorter.

It is evident then that mere dilution will not explain the small number of bacteria found in the general circulation as compared with the number being contributed by the infected vein in some of my cases. Bacteria are evidently killed or very rapidly filtered from the circulation.

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12. Douglas and Haldane (J. Physiol. **56**:69, 1922) and more recently Burwell, Neighbors and Regan (J. Clin. Investigation **5**:129, 1928) gave the rate of the circulation of blood in adult men at rest as from 5 to 8 liters per minute. With increase in pulse rate (through exercise or fever) the speed increases nearly in proportion to the pulse rate and may be as much as 24 liters per minute. As the total volume of blood in a normal adult is variously estimated at from 4,400 to 5,600 cc. (Chang and Harrop: J. Clin. Investigation **5**:393, 1928), the round figure of one circuit per minute assumed for the sake of calculation in the text is a not impossible figure. Probably in our patients, most of whom were children and all of whom had high fever, the actual rate was much faster. This, of course, would only strengthen our argument by shortening the time needed for the general peripheral blood to approach the blood of the local vein in concentration of bacteria.

13. It is interesting to compare this figure with the conclusion of Linhard (Am. J. Physiol. **77**:669, 1926) that after injection of a small amount of a dye solution into a peripheral vein in man uniform distribution throughout the blood occurs in less than five minutes. However, Erlanger (Physiol. Rev. **1**:177, 1921) quoted Douglas as saying that complete mixing takes at least sixteen and a half minutes in man.

The argument to this point has been based on the assumption of a somewhat steady and continuous feeding of bacteria into the blood from the infected focus. However, it has been suggested (Schottmüller,[9] Martin [14] and others) that bacteria are not given off steadily, but in short "showers." If this were the case one would expect to find such differences as occur in my cases (between the number of bacteria in the blood of the vein directly draining the lesion and that of the vein of the arm) only if one happened, by chance, to take blood for cultures exactly at the moment that the "shower" was occurring. For if one took blood for cultures a few minutes after such a "shower," the blood coming directly from the lesion and containing the bacteria would have passed on and mixed in the general circulation, and one would find a more or less uniform distribution of bacteria in all veins.

As it is unlikely that I should by mere accident have made the blood cultures just at the moment of the "shower" in so many of my cases (for at least seven of them showed a very small number of colonies in the vein of the arm, as compared with the jugular vein or veins), it follows that in sinus infections, at least, bacteria are sometimes fed into the blood stream rather continuously or for fairly long periods of time. It is probable enough, of course, that in other cases or in these cases at other times the "shower" mechanism occurs; indeed, in the preceding paper,[11] two cases are discussed in which such a rapid entrance of bacteria into the blood stream was apparently happening at the time of the taking of blood for cultures.

The Points at Which Bacteria Are Possibly Removed.—There are no data at hand to indicate just where the bacteria are removed in human infections. On account of the relative slowness of the bactericidal action, even of immune blood, the possibility that all the rapid disappearance of bacteria is brought about by the blood alone can be discarded.

Since all the returning blood must first go through the capillaries of the lungs before reaching those of the other organs, and since the experiments of Wysokowitsch,[1] Werigo,[2] Bull [4] and others show extensive phagocytosis by leukocytes in the lung capillaries, it seems possible that the lungs may be the primary place of filtration, and that (as in Drinker and Shaw's experiments [6]) the transfer to the reticulo-endothelial cells of the liver and other organs may be secondary. There is also a good deal of indirect evidence from experimental introduction into the circulation of leukocytes laden with carmine or other particles, that the lungs act as primary filters (Aschoff,[15] Christeller and Eisner,[16] Seemann and Theodorowitsch [17]).

14. Martin, Walton: Ann. Surg. **82**:326, 1925.
15. Aschoff: J. Exper. Med. **50**:57, 1926.
16. Christeller and Eisner: Beitr. Path. Anat. u. z. allg. Path. **81**:524, 1929.
17. Seemann and Theodorowitsch: Ztschr. f. d. ges. exper. Med. **69**:742, 1929.

However, even though the circulation of the liver is shunted off from the main blood stream it is possible that the liver may play a primary rôle. The amount of blood passing through it is large. Burton-Opitz [18] found that in a dog weighing 14,300 Gm. the liver, weighing 454 Gm., received 422 cc. of blood per minute. If one accepts Haldane and Smith's and more recently Linhard's [13] ratio of the total blood as approximately one-twentieth of the body weight, the blood going through the liver per minute would be actually more than half the total volume. And we know from Manwaring and Coe's [7] experiments, referred to, how complete the filtration of bacteria by the liver can be. This is borne out for human pathology by clinical observations on pylephlebitis. In this condition bacteria are practically never found in the peripheral blood (Libman [19]). The enormous numbers in the portal vein are all filtered out by the liver.

TABLE 3.—*Comparative Number of Bacteria in Radial (or Brachial) Artery and in Vein of Arm*

Case	Diagnosis and Organism	Colonies per Cc. in Artery	Colonies per Cc. in Vein,
39	Endocarditis; Streptococcus A	285	200
38	Sinus thrombosis; Streptococcus B	1 or 2	2 or 27*
37	Endocarditis; Streptococcus A	6	4
36	Endocarditis; Gonococcus	5	3
35	Endocarditis; Streptococcus A	10	10

* This case, which is fully discussed in the preceding paper,[11] is given here for the sake of completeness, but is disregarded in the discussion because there was so much delay before the two arterial punctures that the cultures from the arteries were not truly simultaneous with those from the vein. It is regarded as an instance in which a "shower" of bacteria was being rapidly removed from the blood.

Evidence That Peripheral Tissues Are Not Site of Filtration.—While I can offer no evidence as to the particular organs in which the bacteria are filtered out in human disease, I can offer proof that they are not removed by the peripheral tissues of the extremities.

In four cases of bacterial endocarditis and in one of sinus thrombosis, I have done simultaneous blood cultures from a brachial or radial artery and from one or more peripheral veins (see table 3). In these cases the number of colonies in the vein was not significantly smaller than in the artery; i. e., the differences noted were within the range of possible error of the method, and if there was any filtration of bacteria in the capillaries of the hand and forearm it was not detected. I have not made comparative observations on carotid artery and jugular vein or on femoral artery and vein. But since, as pointed out, the six cases of bacterial endocarditis showed approximately equal numbers of bacteria in the two jugular veins and the vein of the

18. Burton-Opitz: Quart. J. Exper. Physiol. **4**:116, 1911.
19. Libman: Am. J. M. Sc. **136**:548, 1908.

arm or (in the one case so tested, in the two femoral veins and vein of the arm), and as the two cases of bacteremia from phlebitis of centrally placed veins (hypogastric, axillary) showed the same, it is probable that few bacteria are removed from the blood by the brain and meninges or by the lower extremities.

These observations do not rule out a possible extensive removal of bacteria from the blood by the bone marrow, such as has been experimentally demonstrated in animals (Parker and Franke,[20] Adler and Singer[21] and others). In our cases the veins aspirated did not drain a sufficient area of bone marrow to lead one to expect demonstrable effects from this cause.

CONCLUSIONS

Observations are presented to show that in cases of sinus thrombosis bacteria are rapidly filtered out of the circulating blood. Reasons are given for believing that in many of the cases bacteria are fed into the blood stream from the lesion in the vein somewhat steadily over a period of time rather than in momentary "showers." Observations on the number of bacteria at any moment in the blood of an artery and a vein of an extremity show that there is little or no filtration of bacteria by the peripheral tissues.

20. Parker and Franke: J. M. Research **39**:301, 1919.
21. Adler and Singer: Med. Klin. **210**:429, 1925.

General Review

THE PLASMA CELL

A CRITICAL REVIEW OF ITS MORPHOGENESIS, FUNCTION AND DEVELOPMENTAL CAPACITY UNDER NORMAL AND UNDER ABNORMAL CONDITIONS *

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CONTENTS

The literature on the plasma cell is large and controversial. Downey (1911), Gruner (1913), Ferrata (1918), de Asua (1922), Kingsley (1924), Maximow (1928) and others, including myself (1929), have variously presented accumulated data pertaining to the plasma cell, but in the light of Jordan's recent unique hypothesis that plasma cells are aborted erythroblasts, a detailed presentation of the history of this cell for purposes of orientation seems again to be called for.

Before giving the following survey, I shall call attention to a comprehensive and excellent review on the plasma cell published some years ago in Spanish by Jimenez de Asua (1922). His work and that of Downey, Ferrata, Maximow and myself on the literature may be summarized as follows:

VIEWS OF CAJAL, UNNA AND MARSCHALKÓ

Although not generally known, the plasma cell was discovered and accurately described by Ramon y Cajal in 1890. He encountered the structure in syphilitic condylomas and named it the cianophil cell, a term still adhered to by the present Spanish school of investigators.

* Submitted for publication, Jan. 20, 1931.

* From the Laboratory of the Daniel Baugh Institute of Anatomy, Jefferson Medical College.

Priority in using the term "plasma cell" for the same structure belongs to Unna, who, in 1891, used the name in describing a cell seen by him in the skin of patients with lupus. It is interesting to note that Unna himself, in 1903, graciously conceded priority in the discovery of the cell to Cajal.

Cajal originally described the cianophil cell as a spherical or elipsoidal structure, varying in diameter from 7 to 14 microns. Its protoplasm was characterized by a deep staining reaction with aniline dyes and the presence of round vacuoles. Its nucleus was pictured as spherical, with a distinct chromatic network and a nearly constant excentric position (su situación es casi siempre excentrica). Since, in morphology of nucleus and vacuolization of protoplasm, Cajal was unable to find an analogous type of cell among the then known leukocytes, he was inclined to regard the structure as a special embryonic cell (Nunca hemos visto en tales células núcleo análogo al de los leucocitos, por lo cual y por su vacuolización protoplásmica nos inclinamos a estimarlos como células embrionarias especiales).

Regarding the division of the plasma cell, Cajal stated that not infrequently some of these corpuscles might be met with in direct proliferation, but he never saw in them signs of karyokinesis. In 1896, Cajal maintained that the cells were normal constituents of the connective tissue, that they originated from tissue lymphocytes, that the perinuclear area contained a reticular apparatus of Golgi, and finally, that in tumors, epitheliomas and papillomas, the cells could transform into fibroblasts. The latter theory he, however, no longer stressed in his final publications.

Unna (1891), using a technic of polychrome azure and successive decolorization with glycerin-ether, encountered structures in the skin in lupus, which because of their especially pronounced basophil protoplasm, he called plasma cells, a term which had already been used by Waldeyer (1875) to designate a variety of nonrelated, deep-staining connective tissue cells.

From 1891 to 1908 in various investigations and treatises, Unna insisted that the most salient characteristic of the plasma cell was the deep basophilia of its protoplasm, rather than the specific structure of its nucleus, as Marschalkó in the then current literature repeatedly asserted. The cell, according to Unna, was unusually large, oval or cubic in form, its principal characteristic residing in its peculiar protoplasm which, in addition to staining intensely with such basic dyes as methylene azure and pyronin, showed a constantly present, vague granulation (amorphkörnig), which he termed granuloplasm. The latter was regarded as specific for the plasma cell, since other connective tissue cells had an alveolar type of protoplasm (spongioplasm). The nucleus of the plasma cell, usually oval in outline, was depicted as having prevailingly a clear

aspect and a network composed of coarse chromatic strands. Mitosis being rare, the cell divided by amitosis, thereby giving rise to binucleated structures. Genetically, the cell was derived from fixed connective tissue elements by way of unilateral hypertrophy. While, accordingly, a specific type of cell, it, nevertheless, occurred only under pathologic conditions, especially of the chronic variety.

Unna's description of the cell was soon modified by the investigations of Jadassohn (1891-1893), who demonstrated the presence of plasma cells in lymph follicles and lymph glands in man and other animals. He denied the specific character of the granuloplasm and insisted on the paramount importance of a definite chromatic pattern and an excentric position of the nucleus.

This phase of the problem was preeminently taken up by Marschalkó (1895), for whom the morphology of the nucleus and not the basophilia of the protoplasm (Unna) was the deciding specific criterion for the cell. A granuloplasm did not exist; at most, there was a realization of a mottled (crumbled) aspect of protoplasm (Jadassohn), a condition which he tried to portray by the term "Krumelzellen." After extensive observations on normal, pathologic and experimental material, Marschalkó gave the following characteristics as essential for the cell:

1. Primarily a specific type of nucleus, small in size, round or oval in contour, with from five to eight distinct, deep staining, angular blocks of chromatin regularly arranged in a circle about the nuclear membrane. (Since this chromatic pattern simulated the disposition of spokes of a cartwheel, Pappenheim later introduced the term "Radkern" to cover the Marschalkó type of nucleus.)

2. An almost constant, eccentric position of the nucleus (admitted later by Unna).

3. A perinuclear lighter staining area, due to an accumulation of protoplasm at the periphery of the cell.

4. A spherical, at times irregular, protoplasm, which although nonhomogeneous, is, nevertheless, devoid of any specific granuloplasm.

The cells, according to Marschalkó, were not pathologic, but normal, constituents of the connective tissue. They did not arise from the latter, but were formed from emigrated hemic lymphocytes, and this for the following reasons: In foci of infiltrations artificially produced, the number of plasma cells was so great, and their appearance so sudden, as to exclude a possible origin from tissue elements. There was an absence of transitional stages between fibroblasts and plasma cells. Lymphocytes, when grouped about the wall of a blood vessel, were so arranged that plasma cells occupied the outermost regions of the infiltration, while lymphocytes were nearest to the vessel. In aseptic reparative processes plasma cells were never seen. In leukocytosis, experimentally produced with tubercular or bacterial proteins,

plasma cells and transitional stages were plentiful in blood vessels. With Biondi staining, the nuclei of connective tissue cells were violet, while those of lymphocytes and plasma cells were green. Finally, according to Marschalkó, plasma cells, although a specific type of cell, could transform into fibroblasts, especially in new-formed tissue.

SUBSEQUENT INVESTIGATIONS

The opposing, yet, as it were, guiding, views of Unna and Marschalkó gave rise to numerous investigations and frequent polemical discussions. While initially Almkvist (1901) and Schlesinger (1902), later Pappenheim, tried to reconcile the two conflicting theories by the assertion that there were two types of plasma cells, those of Unna and those of Marschalkó, subsequent investigations finally led to a precise categorization of the cell as to specific morphology, genesis and functional variation.

The specificity of Unna's granuloplasm, upheld by Downey (1911), was originally denied by Jadassohn and Marschalkó and seemingly definitely disestablished by the investigations of Marchand (1913), who showed that a granuloplastic aspect of protoplasm was not peculiar to plasma cells, but due to a transient cytoplasmic basophilia present in a variety of tissue elements other than plasma cells. De Asua (1922), Maximow (1928), Jordan (1929) and others denied the specificity of the granuloplasm, Jordan in particular claiming it to be an artefact. The latter interpretation, however, was not accepted by Gruner (1913), who quoted Schridde as having observed the granuloplasm in frozen sections of fresh tissue. Gruner further quoted Pappenheim to the effect that the granuloplasm consisted of a paranucleoproteid which was "strongly acid, and readily soluble in saline."

De Asua (1922) attempted to solve the problem by asserting that plasma cells were secretory corpuscles, the cyclic changes of which were morphologically expressed in the following types of cytoplasm: (1) pulverized and uniformly basophil (a resting stage), (2) crumbled or mottled (accumulation of secretion in granule form), (3) filamentous (a forestage to plasmorrhexis) and (4) peripherally serrated (stage of secretion). In addition to these, de Asua recorded two degenerating types, viz., those with vacuoles and those with hyaline body formation.

Recently Kingsley (1924) spoke of a distinct, homogeneous granuloplasm in plasma cells. Aside from regarding it as the first sign of the formation of the plasma cell from the fibroblast, he does not commit himself as to its specific nature or significance.

The contention of Cajal and Marschalkó that plasma cells are normal components of the connective tissue was soon substantiated by Schottländer (1897), who observed them in the ligament of the normal ovary; by Jolly (1900), Schwarz (1905) and Maximow (1902-1906), all of

whom described them as characteristic structures in the great omentum; and by Dominici (1901) and Schlesinger (1902), who found them abundantly in the intestinal mucosa. Since then, various workers, especially Maximow, Ferrata, Weidenreich, Downey and Jolly, have shown them to be normally present in the interstitial tissue of various organs and glands (mammary and submaxillary glands, tonsils, liver, kidneys, bone marrow and lymphoid tissue). Few in the circulating blood, normal or pathologic (Ferrata, Piney), sparse in loose connective tissue (Maximow), their presence in the embryo was denied by Schridde (1921), Ferrata and myself (1923) and Maximow (1928).

THE CELL IN LOWER VERTEBRATES

Respecting lower vertebrates, Soluch (1908) showed that plasma cells are abundantly present in the connective tissue of birds, an observation recently confirmed by Mjassojedoff (1926) for the adult hen. Downey (1911) reported high ratios of plasma cells, many of which were atypical and of clasmatocytic origin, in amphibia, reptiles and fishes. He found them to be particularly numerous in the lymphorenal tissue of the ganoid fish polyodon, in the lung of the garter snake and in the mesentery of the frog. I examined many species of cold-blooded animals, and contributed data (1924) which indicated an apparent absence of the plasma mast cell in lower forms. According to Jordan and Speidel (1929), plasma cells are numerous in the splenic sinuses of the horned toad.

THE PERINUCLEAR AREA

Theories regarding the nature of the perinuclear lighter staining area (astrospheric region) in the plasma cell varied considerably. Marschalkó considered it as an essential criterion of the plasma cell. Unna, however, contended that, since it was caused by a washing out of granuloplasm, all cells having such an area were in a state of incipient atrophy, a point of view confirmed later by Greggio (1909) and Papadia (1910). Joannovics (1899) and Schaffer (1910) maintained that the area represented a portion of the cytoplasm devoid of basophil substance, an interpretation somewhat similar to that of Dubreuil (1909), who claimed that the perinuclear cytoplasm was homogeneous and vitreous. The most probable opinion, viz., that the area constitutes the specific sphere of attraction of the cell, with content of centriole group, was first established with iron-hematoxylin staining by Maximow (1902-1906) and subsequently corroborated by Weidenreich (1909), Wallgren (1911), Jolly and Ferrata. Cajal (1896), as stated, had shown that this area contained a distinct Golgi apparatus. Downey (1911) regarded the area as the seat of initial elaboration of fuchsinophil bodies. Gruner

(1913) quoted Proell as having observed lipoid granules in the astrospheric region, also Loele as recording the presence of much phenolphil substance near the nucleus.

VACUOLES

Cytoplasmic vacuoles in plasma cells, originally noted by Cajal, were later shown to vary in number, content and distribution. Some investigators interpreted them as degeneration phenomena (Unna, Krompecher, Papadia, de Asua); others regarded them as representing temporary secretory cell states (Weidenreich, Downey). Their nonartefact nature was established by Dubreuil and Favre (1920) in staining them supravitally with neutral red. Dubreuil (1909), later Dubreuil and Favre (1920), also Wallgren (1911), Downey (1911), Schridde (1929) and Bloom (1928), demonstrated in these vacuoles the presence of round, granular or rod-shaped structures (mitochondria, Schridde-Altmann granules). According to Bloom (1928), the presence of a typical well developed roset in the plasma cells, revealed with supravital neutral red staining, "deprives the rosette of its importance as a specific criterion of monocytes," as claimed by Cunningham, Sabin and Doan (1925). Recently Forkner (1930), after examining supravitally stained preparations of lymph nodes of rabbits, repudiated Bloom's observation, stating that in no instance do plasma cells possess the segregation granules characteristic of monocytes.

DIVISION

Regarding mitotic division of plasma cells, Cajal first stated that this took place very rarely, an opinion confirmed by Unna, Ferrata, Krompecher, Maximow, Globus and myself and others; Maximow and Globus and I asserted that when such a division did occur, it was nearly exclusively in young plasma cells. Schridde (1921), on the other hand, seemingly held mitosis as frequent, especially in the plasma cells of perivascular infiltrations.

Indirect division, i. e., amitosis or amitotic constriction of nucleus with resultant binucleated or trinucleated structures, has repeatedly been reported as a frequent phenomenon in plasma cells (Maximow, Weidenreich, Downey, Dubreuil and Favre, de Asua, Globus and myself). Maximow (1902) regarded the process as peculiar to old, i. e., degenerating, cells, an observation which I also made on the cells in perivascular infiltrations.

According to Verrati, direct nuclear division without accompanying cytoplasmic division explains the origin of the large multinucleated (from five to eight) plasma cells, originally referred to by Cajal. On the same basis Krompecher explained the formation of giant plasma cells, the existence of which was also admitted by Ferrata.

ATYPICAL PLASMA CELLS

References to the literature have thus far in this review concerned typical plasma cells. On the occurrence of atypical plasma cells, a point especially emphasized by Weidenreich, Downey, Pappenheim, Naegeli and Maximow, the following observations are to be listed: As early as 1895 Hodara grouped basic staining cells into plasma cells and pseudoplasma cells. This procedure was followed by Papadia (1910) in his large work on experimental encephalitis, in which even endothelial cells were reported as displaying a plasma cell aspect, but because of nuclear differences were termed pseudoplasma cells.

Pappenheim (1901-1920) perhaps reached the greatest extreme in claiming that all lymphoid cells, whether of lymphoblastic or myeloblastic origin, may transform into plasma cells (plasmocytes); hence his intricate, practically self-guiding terminology of macrolymphocytic plasmocyte, leukoblastic macroplasmocyte, lymphocytic microplasmocyte, microleukoblastic plasmocyte, etc. Gruner (1913), adopting Pappenheim's view, gave a similar list of possible plasma cells. In another posthumous work (1919) Pappenheim textually (p. 188) stated that plasma cells are to be regarded as inflammatory, altered histogenous lymphocytes of granulation tissue (entzündlich veränderte histiogene Granulationsgewebslymphocyten). In spite of this seemingly restrictive categorization, in the same work are depicted many figures of plasma cells which include manifold transitional stages from lymphocytes and monocytes, leukoblasts and lymphocytes to plasma cells.

Opposed to the extreme position of Pappenheim, Maximow (1902), Schwarz (1905), Weidenreich (1909-1910) and Downey (1911) maintained that atypical plasma cells may differentiate from a restricted quota of lymphoid cells (polyblasts, lymphocytes, clasmatocytes), Weidenreich perhaps coming closest to the contention of Pappenheim with the statement that since the plasma cell condition (Plasmabeschaffenheit) is a transient, functional, i. e., irritative, physiologic condition, it may occur in various lymphoid cells, perhaps even in lymphoblasts. Downey (1911), in a comprehensive study of plasma cells, adopted a similar view, stating that "plasma cells are differentiated from all types of lymphoidal cells." Convinced on comparative cytologic evidence that there are plasma cells having morphologic characteristics other than those given by Marschalkó, he included as additional precursors of plasma cells, the perithelial cells of Marchand, the resting wandering cells of Maximow (clasmatocytes), the large leukocytoid lymphocytes, the large mononuclears (even those coming from the mesothelial cells of the mesentery) and possibly, a small percentage of fibroblasts.

Supporting Pappenheim's view are the views of Schridde (1902), Gruner (1913), Huebschmann (1913), Naegeli (1919), McGowan

(1928) and Piney (1928), all of whom admitted the occurrence of typical lymphoblastic plasma cells as originally stated by Hodara. Türk went still farther by including as plasma cells his "irritation forms," cell types usually regarded as pathologically altered myeloblasts (Naegeli, 1919). Gruner (1913) adopted Türk's view in claiming that the irritation forms are tissue plasma cells which entered the blood stream. Recently Downey (1924-1928), in an extensive study on the myeloblasts, admitted a differentiation of plasma cells from myeloblasts, but stated that while the nuclear pattern of the latter may remain unaltered during the transformation, "frequently its chromatin becomes exaggerated into coarse masses and then it is difficult to tell whether the plasma cell has been derived from a large lymphocyte or a myeloblast."

That the "irritation forms" of Türk, described by him as characteristic for pathologic, especially leukemic, blood, have no relation to plasma cells was, in the opinion of Ferrata, definitely established by two of his pupils, Juspa and Negreiros-Rinaldi (1913). In studies of blood and bone marrow they demonstrated the nuclear differences in the two types of cells, interpreting the "irritation forms" as developmentally inhibited hemocytoblasts. It was further shown by Ferrata and myself (1923) that the occurrence of Türk cells, as well as of Rieder cells, is not necessarily restricted to pathologic conditions, since both types may be encountered as normal constituents of embryonic blood, viz., that of the prehepatic period. Because of the extreme sparsity of Türk cells, Naegeli suggested that the term "irritation form" be dropped.

Seemingly still dubious is the position of the lymphoblastic plasma cell. Foa (1902), in a case of typhus, encountered lymphoblast-like plasma cells in splenic follicles, but regarded the reaction as pseudoplasmatic, since in respect to nuclear morphology the deep-staining cells in no way corresponded to plasma cells. Naegeli (1919), on the other hand, selected lymphoblastic plasmic cells as one kind in a classification of four possible types (the others being lymphocytic, "Radkern" and myeloblastic). In the blood of patients with measles he observed 30 per cent lymphoblastic plasma cells and quoted Hildebrandt as having reported 17 per cent for the same malady.

Of paramount importance in this respect is the position taken by Ferrata. In his large work he repeatedly emphasized the fact that if deep basophilia of protoplasm alone is considered the specific criterion of the plasma cell, then one can equally well include in this category various nonrelated lymphoid cells, even the progenitors of the erythrocytes. (Con questo criterio allora una grande quantita de cellule a tipo linfoide, compresi i progenitori degli eritrociti, potrebbero venire confuse colle plasmazellen.)

The quotation brings me to the most recent speculations regarding the plasma cell. Thus McGowan (1926-1927), on the assumption that the term plasma cell is "rather a morphological than a physiological one," postulated the formation of lymphoblastic, monoblastic, myeloblastic and even erythroblastic plasma cells by way of aberration from primitive stem cells. Jordan (1929) and Jordan and Speidel (1929) and presumably Dawson and Masur (1929) interpreted plasma cells as aborted hemoblasts, i. e., erythroblasts or granuloblasts that failed to differentiate into normal red corpuscles or granulocytes. In contrast to these writers Piney (1928) followed the commonly accepted interpretation that plasma cells are modified lymphocytes, but postulated the occurrence of lymphoblastic plasma cells under morbid conditions.

ORIGIN OF PLASMA CELLS

As opinions have varied in respect to the specific morphology of the plasma cell, so likewise have they differed as to its histogenesis. The theories advanced may be briefly summarized as follows:

1. A histogenous origin from connective tissue cells, including tissue lymphocytes, fibroblasts, clasmatocytes, resting wandering cells, adventitial cells, hemohistioblasts, etc.: Unna (1891), Cajal (1896), Pappenheim (1901-1920), Marchand (1901), Dominici (1901), Foa (1902), Türk (1904), Morandi (1904), Verrati (1905), Ehrlich (1904), Greggio (1909), Papadia (1910), Downey (1911), Ferrata (1918), de Asua (1922), Lewin (1929), Rogers (1930) and Kingsley (1924). Kingsley emphasized especially a fibroblastic origin, since Downey (1911) had stated that "the plasma cells formed in this way are not numerous and it is still a question as to whether they ever develop into the typical Marschalkó type."

2. A hematogenic origin from emigrated lymphocytes: Marschalkó (1895), Schottländer (1897), Krompecher (1898), Else von der Leyen (1901), Enderlen and Justi (1901), Schlesinger (1902), Nissl (1904), K. Ziegler (1904), Cerletti (1907), Naegeli (1919) and Jolly (1923).

3. Mixed origin from emigrated lymphocytes (monocytes) or preexistent tissue lymphocytes: Ribbert (1897), Joannovics (1899), Maximow (1902), Schridde (1905-1921), Weidenreich (1911), Downey (1911), Dubreuil and Favre (1920), Bloom (1928), Globus and myself (1929).

4. An origin from immature blood cells (myeloblasts, hemoblasts [erythroblasts, granuloblasts]) through aberration or abortion: McGowan (1928), Jordan (1929), Jordan and Speidel (1929) and Dawson and Masur (1929).

Regarding tissue cultures, Maximow (1922-1923) showed that in explants of lymphoid tissue plasma cells develop from local lymphocytes in the course of two days. In cultures of leptomeninges the same phenomenon was noted, being particularly marked in lymphocytes having a periarterial habitat.

PROGRESSIVE AND REGRESSIVE CHANGES IN PLASMA CELLS

Degenerative Changes—Russell Bodies.—In summary, the degenerative changes recorded in the literature have been the following:

1. Homogeneous Degeneration: This process is characterized by an uneven, varyingly feeble staining capacity, at times a nonstaining capacity, on the part of the cytoplasm of the plasma cell, while the nucleus remains relatively intact. According to Unna, it is accomplished through separation of the granuloplasm and fragmentation of the spongioplasm. For Schridde, Maximow, Jolly, Kingsley, Globus and myself, degeneration is the ultimate fate of the vast majority of plasma cells. They are brought into existence only to undergo degeneration, the associated phenomena of which are pyknosis and fragmentation of nuclei, with frequent formation of acidophil bodies.

2. Hyaline Degeneration: This is exemplified in the formation of intracellular hyaline (acidophil) bodies, commonly known as Russell bodies (1890). Unna spoke of the phenomenon as a hyaline metamorphosis of the granuloplasm effected by a combination of the acid substance of the latter with a basic albuminoid substance present in the interstitial lymph. This opinion, confirmed by Fick (1908), was objected to by Papadia (1910), who stated that since in number and in mass the hyaline globules far exceed the protoplasmic dimensions, their origin is perhaps due to a cytoplasmic pathologic secretion, which on accumulation is extruded. Gruner (1913) cited Miller (1910) as considering Russell body formation to be a myelin degeneration of cell substance.

Numerous workers, Pappenheim, Ferrata, Jolly, Maximow, Downey, Schridde, de Asua, Kingsley, Jordan and Speidel and others, including myself, showed that Russell body formation is a constant phenomenon in degenerating plasma cells, and that at necrobiosis of the latter the bodies become freely dispersed into the tissues. In syphilitic material these acidophil bodies were shown to vary in size from small eosinophil, granule-like structures to giant spheres of monocyte proportions (Globus and myself). According to Schridde (1921), Russell bodies make their first appearance in the form of fine bluish, gentianophil granules, which then through growth and confluence give rise to the larger and more characteristic structures. With safranin and methyl green staining, according to Pappenheim (1919), the bodies appear red in a background of green. Downey (1911) gave similar pictures.

That Russell bodies are pathologic secretions of plasma cells was recently again advocated by de Asua (1922). According to Downey (1911), the structures "probably represent a special kind of secretion or the accumulation and thickening of the normal secretion," a view likewise recently suggested by Kingsley (1924). Decidedly new was the speculation of Jordan and Speidel (1929), according to whom Russell

cell bodies "represent hemoblasts (erythroblasts or granuloblasts) which failed to transform normally into erythrocytes or granulocytes." Dawson (1929) was inclined to favor a similar view.

3. Vacuolar Degeneration: This process, noted by Cajal, Unna, Pappenheim, Krompecher, Papadia, de Asua and others, is characterized by the presence of unstainable areas, which give the cell a foamlike aspect, hence the term "Schaumzellen" employed by different authors (Pappenheim). Schridde interpreted the process as a mucoid degeneration, while Unna and Papadia regarded it as due primarily to a change in water content. Since this type of degeneration was reported as frequent in condyloma (Cajal), likewise in dementia paralytica (Franca and Athias, 1902), Pirone (1909) suggested that it was peculiar to aged cells. In Pappenheim's last work, "Schaumzellen" are regarded as former histogenous phagocytic monocytes from which the Russell bodies have become extruded.

4. Pathologic Degeneration: Krompecher stated that pathologic degeneration occurs especially during inflammatory processes and is characterized by important nuclear changes, viz., vesicular aspect, uniform color, a less distinct chromatic network, with one or two central blocks. In the opinions of Bosellini and Papadia, it was the viewing of this type of degenerating nuclei in lupus material which prevented Unna from properly evaluating the essential importance of nuclear structures as outlined by Marschalkó.

5. Hemoglobiniferous Degeneration: The hypothesis of Jordan, Jordan and Speidel, and, presumably, of Dawson, of a hemoglobiniferous degeneration is based on the view that aborted erythroblasts become plasma cells and as such gather the initially elaborated hemoglobin into globules, thereby forming Russell bodies. McGowan's theory may be incorporated under this heading, for the aberrated erythroblastic plasma cell, according to him, has hemoglobin in its cytoplasm. A genetic relationship between plasma cells and erythroblastic formations was denied by MacMillan (1928) and Forkner (1930). The former found no evidence for it in lymph nodes of rats rendered anemic; Forkner contended that although plasma cells in supravitally stained preparations of lymph nodes have a homogeneous protoplasm exhibiting a faint yellow tinge similar to that existent in developing red cells, the conclusion cannot be drawn that, therefore, they are developing erythrocytes, since other criteria distinguish them from the latter.

Progressive Changes—Plasma Mast Cells.—The following developmental potencies have been ascribed to plasma cells:

1. Formation of Plasma Mast Cells: This process, accomplished through an endogenous differentiation of basophil, metachromatic gran-

ules in otherwise unaltered plasma cells, was first reported by Krompecher (1891), who observed it in mammary cancer and endotheliomas of the skin. The observation was subsequently confirmed in various other material by Marschalkó, Schwarz, Weishaupt, Pappenheim, Weidenreich, Downey, Sabrazès and Lafon, Martinotti, Greggio, Weill and others. Of recent workers, Ferrata (1918), Schridde (1921) and de Asua (1922) denied the formation, while Dubreuil and Favre (1920) and Globus and myself (1929) reaffirmed it.

2. Elaboration of Other Granules: Thus, according to Schridde (1905), a very large proportion of plasma cells elaborate neutrophil granules; 1 in 1,000 develops eosinophil granules, while 1 in 2,000 forms basophil metachromatic granules. Regarding the latter, Schridde, in a recent contribution (1921), asserted that cells having the cartwheel nucleus and basophil granules are not to be classified with plasma cells; i. e., they are not plasma mast cells, but ordinary mast cells the nuclei of which have undergone peripheral hyperchromatic changes similar to those seen in erythroblasts and various other cells. In the same work, Schridde maintained that, while the majority of plasma cells contain Altman granules, a certain quota have fine bluish gentianophil granules, the precursors of Russell bodies. Naegeli's opinion, viz., that some plasma cells contain azure granules, was denied by both Pappenheim (1920) and Ferrata. Dubreuil and Favre described, in certain plasma cells, eosinophil granules, in others secretory granules similar to those found in gland cells.

3. Transformation of Plasma Cells into Fixed Connective Tissue Elements: Marschalkó held the transformation of plasma cells into fixed connective tissue elements to be true, especially in new-formed tissue, an opinion shared by Gruner (1913), who claimed that with scar formation the local plasma cells become fibroblasts. Cajal reported transitional stages leading to the formation of fibroblasts in tumors, papillomas and epitheliomas. Whereas, in his last publication Cajal was inclined to doubt this developmental potency, de Asua (1922) seemingly reaffirmed it. Schottländer and Krompecher, although both advocates of a hematogenic origin of plasma cells, stated that the latter could transform into fixed connective tissue elements and epithelioid cells, a theory fully subscribed to later by Ravenna (1906). Recently, Kingsley (1924) admitted a heteroplastic development of plasma cells from tissue lymphocytes and fibroblasts, but denied a reversion of such formed plasma cells to parental stages.

SPECULATIONS ON FUNCTION

Joannovics (1899) and Schaffer (1901) contended that since plasma cells appear wherever there is destruction of nuclei, their formation is

due to local absorption of chromatic material; incidentally, they thereby help to remove cellular metabolic products.

Bosellini (1902) advocated the quaint theory that the stainable material in plasma cells is nucleic and destined for the formation of new nuclei.

Enderlen and Justi (1901), also Porcile (1904), believed that the cells were carriers of nutritive material, a point of view partially taken by Dantschakoff (1905) in maintaining that in the submaxillary gland plasma cells, after absorption of substance from the blood and lymph, transmit it to epithelial cells. At one time, Pappenheim (1905) interpreted the formation of plasma cells as caused by a pathologic overnourishment (hypertrophy) in connective tissue cells. Recently Kingsley (1924) favored a similar view. On the hypothesis that the peculiar appearance of the granuloplasm of the plasma cell is due to iron content (Harris), Gruner (1913) suggested that the iron in question might possibly "bear some relation to the formation of fibrous tissue secretion."

Weidenreich (1909-1911) proposed the solution that the pronounced basophilia of plasma cells is due to a transient, irritative physiologic condition in lymphocytes; that the cells are secretory corpuscles, as evidenced by extensive cytoplasmic budding and loss of these by clasmatosis to adjacent tissues. Downey (1911) confirmed this point of view, especially for the plasma cells in lower vertebrates. De Asua (1922) upheld it as true for all plasma cells, save those exhibiting vacuolar and hyaline degeneration.

Huebschmann (1913) regarded plasma cells as elements capable of elaborating a defence (antitoxic) substance. A similar view was propounded by Klein (1914) and by Arneth (1920) in maintaining that plasma cells, especially those of chronic disturbances (paralysis, meningitis), are not degenerating cell forms, but functional states of lymphocytes, which, through local toxic activation, are intimately related to immunization processes. Kingsley (1924), on the basis of the large aggregates of plasma cells found in degenerating areas and their mode of origin from local tissue elements, explained their presence as a possible reaction phenomenon, produced by local metabolic changes.

A phagocytic power was ascribed to plasma cells by Nissl (1904), Vanzetti and Parodi (1905), and Gruner (1913). This was denied, however, by Marchand (1902), Morandi (1904) and Greggio (1909).

PATHOLOGIC CONDITIONS

Much of present knowledge regarding plasma cells has been obtained from studies on pathologic material, for the simple reason that, under morbid conditions, especially of the chronic inflammatory type (infiltrations), a marked increase of plasma cells usually takes place. Specific

instances of such increases were listed by the following: Unna (1891), Jadassohn (1891) and Almkvist (1901), in lupus material; Unna (1891) and Bosellini (1902), in granulomas of the skin; Cajal (1896) and de Asua (1922), in tumors, epitheliomas and papillomas; Economo (1920), Marcora (1921) and Globus and myself (1927), in the central nervous system in various forms of encephalitis; Papadia (1910), Vanzetti and Parodi (1905), in those experimentally produced; Foa (1902), in typhus; de Asua (1922), in tuberculous material; Franca and Athias (1902), Havet (1902), Alzheimer (1904), Nissl (1904) and Globus and myself (1929), in the perivascular infiltrations of dementia paralytica; Rogers (1930), in solitary plasma-celled myeloma of bone marrow; Grawitz (1911) and Pappenheim (1919), in the blood of chronic lymphoid leukemia; Klein (1914) and Arneth (1920), in disturbances of the cerebrospinal fluid; Naegeli (1919), in the blood of patients with measles, in which an increase of plasma cells to 30 per cent was recorded.

This topic may be concluded by again referring to the respective positions taken by Maximow, the anatomist, and Naegeli, the pathologist. Maximow repeatedly asserted that wherever an aggregation of lymphocytes and monocytes occurs, there likewise a varying proportion of plasma cells, with transitional stages from lymphocytes and monocytes, may be met with. Naegeli, sharing Maximow's opinion that most plasma cells are modified lymphocytes, recorded them as ubiquitous structures in perivascular infiltrations, granulomas, tumors, etc. A predominance of plasma cells may, in his opinion, lead to: (1) a plasma cell lymphoma, either local or generalized (Frank [1913]), (2) a multiple myeloma of the bone marrow or (3) a specifically distinct plasma cell leukemia, with systemic involvement of the hematopoietic system. In support of the latter view, Naegeli referred in particular to the two cases noted by Ghon and Roman (1913), one of which showed 50 per cent plasma cells in the bone marrow. To these may be added, according to Grawitz (1911) and Gruner (1913), the leukemias of plasma cell type reported in the literature by Gluzinski, Reichenstein, Lusksch, Foa and Michaeli.

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Notes and News

Plant Pathology in the Rockefeller Institute.—The Institute has established a division of plant pathology in connection with its branch for animal pathology near Princeton, N. J. The new division will be in charge of L. O. Kunkel who has been pathologist at the Boyce Thompson Institute for Plant Research at Yonkers, N. Y. The combined laboratories will be known as the Department of Animal and Plant Pathology of the Rockefeller Institute for Medical Research.

Isaac Adler Prizes for Medical Research.—It is reported that Harvard University has been willed $20,000, the income of which is to "provide once in three years a prize for the best piece of original research produced within that period in the United States or Canada on any subject within medical or allied sciences."

New Laboratory at Rockefeller Institute.—This is a seven story structure with two basements which is connected by tunnels with other buildings of the Institute. Five sections of the division of pathology and bacteriology occupy space in the new building.

Anna Fuller Fund.—According to *Science* for April 3, 1931, the "will of Egbert C. Fuller, president of the E. C. Fuller Company, of New York, who died at New Haven on March 5, provides for the establishment of a fund which the executors estimate will reach $1,500,000, to be used 'for alleviation of suffering from disease and especially for the control of cancer.' Mr. Fuller, in his will, directed that the fund be known as the Anna Fuller Fund, in memory of his wife, who died from 'this painful disease.' The fund may be used according to the will only for research as to its cause, treatment and care; the education of the public as to its prevention and treatment and the actual treatment of persons suffering from the disease. While there is hope of preventing cancer, Mr. Fuller provides in his will that the fund shall not be used for the treatment of persons suffering with the disease 'except as incidental to such research and education.' The will also provides for the creation of the Anna Fuller memorial prize which is to be given to any person or persons who 'make a real and outstanding contribution to knowledge of the cause, care and prevention or cure of cancer.' Such award or awards shall not in any five-year period exceed the sum of $25,000. Prizes are to be awarded upon the recommendation of the president of the American Medical Association, the dean of the Johns Hopkins Medical School and the dean of the Harvard Medical School."

New Quarters for Department of Pathology of Long Island College of Medicine.—These quarters consist of communicating floors of the old Hoagland laboratory and the new science laboratory. This space is occupied by the Murray Museum and by preparation and staff rooms. The new students' laboratory is situated on another floor of the new building. A new morgue with a miniature amphitheater seating fifty has been completed and is so designed that the eyes of the furthest spectator are only 13 feet from the table.

DOCTORATES CONFERRED IN HUMAN AND ANIMAL BACTERIOLOGY AND PATHOLOGY BY AMERICAN UNIVERSITIES, 1929-1930

Callie Hull and Clarence J. West, Reprint and Circular Series National Research Council, no. 95, 1930.

Brown: Edwin Munroe Knights, "Observations on Hemolytic Streptococci in Scarlet Fever."

California: James Duncan Brew, "Policies and Results of Sanitary Milk Control."

Chicago: Paul Hardin Harmon, "Observations on the Inoculation of the Smaller Laboratory Animals with the Poliomyelitis Virus." Roland Wendell Harrison, "Experimental Studies upon the Etiology of Influenza." Daniel Allan MacPherson, "Studies on the Metabolism of the Streptococci." Winston Harris Tucker, "Studies on *Clostridium putrificum* and *Clostridium putrefaciens.*" Margaret Jane Pittman, "The Pathogenesis of Experimental Pneumococcus Pneumonia." Denis Raymond Augustine Wharton, "Immunological Studies with Tapeworm Antigens."

Cincinnati: Ethyl Linna Hopphan, "The Study of Dermal Reactions in the Selection of Bacterial Antigens in Biological Therapy."

Colorado: Phillips Thygeson, "The Bacteriology of Trachoma."

Columbia: Ada Ranney Clark, "The Rôle of Clasmatocytes."

Cornell: Gustave Ivar Steffen, "The Gaseous Metabolism of *B. tetani.*" Alexander Zeissig, "A Study of the Complement Fixation Test in the Detection of Acid-Fast Infections of Cattle."

Harvard: John Franklin Enders, "A Study in Bacterial Allergy."

Iowa State College: Irl Donaker Wilson, "A Study of Bovine Coccidiosis."

Johns Hopkins: Shao-Chiung Cheng, "Leucocyte Counts in Rabbits: Observations on the Influence of Various Physiological Factors and Pathological Conditions." Raymond Erl Gardner, "Immunity to Transplantable Rat Tumors with Chicken Blood and Vaccine Virus." Wendell Daniel Gingrich, "Superinfection and Cross-Immunity in Bird Malaria." Kitty H. S. Kempner, "The Influence of Diet upon the Susceptibility of the Rat to an Implanted Sarcoma." Lucile Russell Anderson, "A Study of Bacilli of the Genus *Hemophilus* with Regard to the X and V Growth Factors Under Aerobic and Anaerobic Conditions." Cornelius Alfred Perry, "Bacteriological Analysis of Oysters with Special Reference to the Coli-Aerogenes Group as an Indicator of Fecal Pollution." Marvin Mayer Harris, "A Study of the Bacteriology of Decomposing Crabs and Crab Meat." Minnie Behm Kraemer Harris, "A Study of Spirochetes in Chickens with Special Reference to Those of the Intestinal Tract."

Kansas: Lucy S. Heathman, "Studies of the Antigenic Properties of Some Free Living and Pathogenic Amoebas."

Minnesota: Albert Valentine Stoesser, "Further Studies Concerning the Toxin-Antitoxin Union." Newell Richard Ziegler, "A Comparison of Quantitative Methods for the Determination of Bacterial Populations." Paul Henry Guttman, "Addison's Disease: A Study of the Pathology and a Statistical Analysis." Albert Ernest Kumpf, "A Study of the Blood Proteins and Lipoids with Special Reference to the Changes Occurring in Renal Diseases."

Pennsylvania: M. Gwendolyn Hunsicker Mason, "Tissue Culture Studies Showing the Effect of Diphtheria Toxin, Toxoid, and Toxin-Antitoxin Mixture upon Fibroblasts of Chick Embryo Hearts."

Princeton: Ernest Wesley Blanchard, "An Experimental Study of the Opsonins of the Blood."

Radcliffe: Eva Elizabeth Jones, "Size as a Species Characteristic in *Coccidia:* Variation Under Diverse Conditions of Infection."

Western Reserve: Robert Allan Moore, "The Total Number of Glomeruli in the Kidney of Man and Animals." Henry Welch, "Studies in Ultra Violet Light."

Wisconsin: Rudolph Joseph Allgeier, "Studies in Fermentation." Franklin Ludwig Schacht, "The Hemolytic Streptococcus Content of Milk with Special Reference to the Alpha Type and Mastitis."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

STUDIES ON THE MECHANISM OF WATER EXCHANGE IN THE ANIMAL ORGANISM. F. P. UNDERHILL, R. KAPSINOW and M. E. FISK, Am. J. Physiol. **95**:302, 315, 325, 330, 334, 339, 348, 1930.

In this series of articles there are reported the results of studies of the effect of burns on the animal organism. With superficial burns of the rabbit, there was rapidly produced a marked local subcutaneous edema, which reached its peak in twenty-four hours and did not disappear until the end of the fifth or sixth day. This was accompanied by a marked increase in blood concentration, amounting at times, with a superficial burn of one sixth of the total body surface, to 70 per cent of the total blood volume, and probably to an even greater amount with more extensive superficial burns. The permeability of the local capillaries was greatly affected, as indicated by the passage of dyes into the edematous fluid. The reabsorption of the fluid was slow, after a brief latent period, and substances passing rather freely into the fluid showed little evidence of reabsorption, so that the increased permeability did not operate in both directions. The edematous fluid was practically blood plasma; in both the fluid and the blood serum there was a marked decrease of globulin, which can be explained apparently only as the result of the mechanism of the production of edema, and which may account for the difficulty of water retention in these circumstances. There were, however, certain marked differences in the composition of the edema fluid and the blood serum, the former showing considerably increased amounts of nonprotein nitrogen, potassium, magnesium and inorganic phosphates. Diminution of chloride content in the serum was not observed as long as blood concentration was maintained within normal limits, but this was reduced when the concentration was maintained at a high level. The loss of substance to the edematous fluid did not affect the composition of the tissues with respect to water, ash and chloride content, indicating an apparent conservation of these. Throughout the entire area of the skin there was a great increase of chloride content and of total ash, without, as a rule, any general augmentation of water content. While the accumulation of water in the injured area was dependent on the type of injury, this was not true of the chlorides, which were always greatly increased. The writers infer that the chlorides play a prominent part in the interchange between the blood and the injured tissue. In the case of burned skin, this local increase of chlorides persisted as long as three days; with burned muscle, considerably longer. It was found that with superficial burning, heat might penetrate into the interior cavities enough to raise the temperature appreciably, and so to induce vascular changes apparently sufficient to account for the ulcers, internal hemorrhages, etc. associated with severe burning. Little change of general body temperature was observed, and a rise after twenty-four hours appeared to be due to secondary infection. In animals in which especially severe dehydration was achieved by various methods, it was found that as a result of water deprivation or increased osmotic tension, the body tissues would lose their essential water, with death as an invariable consequence.

H. E. EGGERS.

THE INDUCTION OF THE PSEUDO-PREGNANCY VAGINAL REACTION IN SPAYED MICE BY THE INJECTION OF HUMAN BLOOD. C. F. FLUHMANN, Am. J. Physiol. **95**:422, 1930.

The reaction of the vaginal mucosa of adult spayed white mice after the injection of blood serum was studied with a view to determining the suitability of the test for human diagnostic purposes. It was found that in such mice there was a

mucification of the vaginal mucosa when they were given injections of serum from patients in whom there was known to be a histologic corpus luteum, during pregnancy, early in the puerperium, during the premenstrual stage and accompanying a corpus luteum cyst. However, the same reaction has been observed with blood specimens from the male with one woman after a bilateral oophorectomy and in four women past the climacteric, so that its clinical usefulness would seem improbable.

H. E. Eggers.

Further Observations on the Function of the Gallbladder. A. G. Rewbridge, M. T. Hanke and B. Halpert, Am. J. Physiol. **95**:511, 1930.

A study of the relative times of disappearance of intravenously administered methylene blue from the liver and the gallbladder of dogs showed that it appeared in the bile within thirty minutes, and reached its highest concentration there in one or two hours. It ceased to be present in the bile from the liver about the thirty-sixth hour following its administration; it usually vanished from the contents of the gallbladder from six to twenty-four hours after the cessation of its discharge from the liver. After oral administration, it disappeared in the bile from the liver at about the thirtieth hour, and from the gallbladder some time between the thirtieth and forty-eighth hour after ingestion. It is concluded that exchange of the content of the gallbladder occurs within about twenty-four hours, but this process is retarded when feeding is unsatisfactory.

H. E. Eggers.

Experimental Arteriosclerosis in the Rat. M. Sweeney and E. Smith, Am. J. Physiol. **95**:620, 1930.

Attempts to induce arteriosclerosis in white rats by means of a diet high in salt, and by constant intensive infection over a period of seven months produced by weekly injections of *Staphylococcus aureus*, were unsuccessful. Definite arteriosclerosis, however, was caused by the feeding of approximately 50 cc. of viosterol over a period of twenty-five days.

H. E. Eggers.

Complete Transections of the Spinal Cord at Different Levels. C. P. Richter and M. B. Shaw, Arch. Neurol. & Psychiat. **24**:1107, 1930.

The spinal cord was cut by Richter and Shaw in twenty-four cats to study the effects on the sweat glands. The levels of section of the cord extended from the sixth cervical to the fifth lumbar segment. Total sections severed the pathways of the sympathetic nerves to the sweat glands causing a temporary increase in the resistance of the skin of from 20,000 to 25,000,000 ohms. After from twenty-five to seventy-five days, the resistance curve resumed the initial low level. The effects of the transection differed from those caused by sympathectomy—the former producing a temporary disappearance of the galvanic skin reflex, the latter causing its permanent disappearance. By measuring the conductivity of the skin, the authors believe that it is possible to contrast the effects produced on the sweat glands by a transected cord, sympathectomy and total section of the nerve "and in this way to throw more light on the question of what central and peripheral factors are involved in the control of the sweat glands."

George B. Hassin.

Effect of Acute Experimental Cholecystitis on the Emptying Time of the Gallbladder. G. T. Murphy, Arch. Surg. **21**:300, 1930.

Acute inflammatory processes in the gallbladder were produced experimentally by the intravenous injection of eusol into dogs. In ten experiments, only one instance was encountered in which the acutely inflamed gallbladder showed any evidence of emptying in response to a fat meal.

N. Enzer.

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE) IN IDENTICAL TWINS. W. D. FORBUS and F. S. WOLF, Bull. Johns Hopkins Hosp. **47**:309, 1930.

In the absence of any satisfactory understanding of the origin of these cases of amyotonia congenita as well as of those we have found in the literature, our inclination is naturally to place the greater emphasis on that explanation of the lesions to which there appear the smallest number of objections; and that explanation seems to be the one based on some injury to the developing embryo which localizes especially in the anterior horn of the gray matter of the spinal cord, the condition of the muscles being secondary to this injury. When viewed in this way, amyotonia congenita comes to fall obviously outside of the group of true myopathies.

AUTHORS' SUMMARY.

THE PATHOGENESIS OF THE FORMS OF JAUNDICE. ARNOLD RICE RICH, Bull. Johns Hopkins Hosp. **47**:338, 1930.

In this paper the various forms of jaundice are considered in the light of our present information regarding the physiology and pathology of the formation and excretion of bile pigment. It is pointed out that, from the standpoint of the clinical and pathologic evidence, cases of jaundice are separable, on the basis of pathogenesis, into two main types. The first type, retention jaundice, results from an overproduction of bile pigment, usually associated with conditions (anoxemia, fever, immaturity) which tend to render the excretory power of the liver subnormal; enough bilirubin is therefore retained in the blood to stain the tissues. This form of jaundice is characterized clinically by indirect-reacting plasma bilirubin, increased amounts of fecal urobilin and urobilinuria. Pathologically, the ducts are patent, but the hepatic cells may show atrophy or cloudy swelling, depending on the associated condition of which the jaundice is a symptom. The second type, regurgitation jaundice, is caused by the reflux of whole bile from the canaliculi into the blood stream. This type is characterized clinically by direct-reacting plasma bilirubin, subnormal amounts of fecal urobilin and the presence of bilirubin and bile salts in the urine. The pathologic basis of this form of jaundice is rupture of the canaliculi resulting from obstruction of the ducts or from necrosis of the hepatic cells. Combined forms may occur, as well as a transition from one of these types of jaundice to the other. A classification is offered in which the two types (retention jaundice and regurgitation jaundice) are further subdivided from the standpoint of etiology and pathogenesis, and the reasons for the various subdivisions are discussed.

AUTHOR'S SUMMARY.

THE PRODUCTION OF ACUTE NEPHRITIS BY MEANS OF A PNEUMOCOCCAL AUTOLYSATE. S. S. BLACKMAN, J. H. BROWN and G. RAKE, Bull. Johns Hopkins Hosp. **48**:74, 1931.

Characteristic acute and subacute nephritis has been produced in rabbits by means of an autolysate prepared from type I pneumococcus and also by means of intradermal infection with virulent strains of pneumococci. The toxin affects the glomerular capillaries, as evidenced by the hyaline and fibrin thrombi and by the blood and fibrin in the tubules, and produces injury and necrosis in the epithelium of the tubules and glomeruli. In a certain number of cases the damage to the kidneys has been associated with marked edema of the tissues and with ascites.

AUTHORS' SUMMARY.

EXPERIMENTAL AIR EMBOLISM OF CORONARY ARTERIES. G. RUKSTINAT, J. A. M. A. **96**:26, 1931.

Dogs whose coronary arteries are plugged with air die promptly. In such animals and also in human beings dying of air embolism, there are no lesions demonstrable anywhere to explain death unless an exception is made of the presence of air in the blood. In air embolism of the coronary arteries, either

recovery or death takes place promptly. Direct cerebral air embolism through the carotid arteries is succeeded by cerebral irritation which does not develop in dogs with solely coronary air embolism, although both may have apparently similar amounts of air in their leptomeningeal vessels. Delayed cerebral air embolism was not observed in dogs recovering from coronary artery air embolism.

AUTHOR'S SUMMARY.

THE ANTIRACHITIC ACTION OF COD LIVER OIL AND IRRADIATED ERGOSTEROL. A. M. PAPPENHEIMER, J. Exper. Med. **52**:805, 1930.

Cod liver oil and viosterol in therapeutic doses are antirachitic in rats in the absence of the parathyroid gland, or of the thymus, or of both.

AUTHOR'S SUMMARY.

MOUSE LEUKEMIA. M. N. RICHTER and E. C. MACDOWELL, J. Exper. Med. **52**:823, 1930.

Several lines of lymphatic leukemia in mice, experimentally transmitted by inoculation into hosts of a closely inbred strain, have been established and carried on simultaneously. Among the inoculated mice there were found different types of response, according to the line of leukemia inoculated. The differences consisted mainly in the extent or distribution of lesions. Although the same line did not always show the same distribution of lesions, there was a distinct tendency for the cases in a line to present the same characteristics on successive transfers over a considerable period. The lesions characteristic of a line were not necessarily those present in the spontaneous case from which the first transfer of the line was made. As the mice used for inoculation were genetically uniform, the differences between the lines are not due to genetic differences in the hosts, but to differences in the materials inoculated.

AUTHORS' SUMMARY.

THE RELATIVE REACTION WITHIN LIVING MAMMALIAN TISSUES. H. P. GILDING, J. Exper. Med. **52**:949 and 953, 1930.

The distribution and segregation of highly colloidal vital dyes follow definite lines irrespective of the pigment employed, the localization of one dye differing from that of another only in details. Erythrolitmin well exemplifies this rule. The minutiae of the staining here reported are not unique, nor indeed are they peculiar to extraneous pigments. The granular localization in cardiac muscle resembles that seen in brown atrophy of the heart, while the general distribution of erythrolitmin has similarities to that of the pigments present in clinical and experimental hemochromatosis. There is reason to suppose that the abundance of pigment in the parenchyma of the liver in this disease is the result of hepatic damage. Taken together, the facts give ground for the supposition that the morbid pigments just mentioned are segregated within the body by the same processes as are the highly colloidal "acid" dyes, a view already put forward by von Möllendorff.

By a variety of methods, necrosis of individual cells was produced in the living animal. The death of the cells was found to be clearly perceptible by means of the changes in the color of segregated erythrolitmin at a time when it was not yet recognizable by ordinary histologic methods. The hue of the dye pointed to an alteration in the direction of alkalinity; but the extent of this could not be determined owing to the limited range of the indicator. Cartilage damaged by freezing in situ becomes alkaline, its reaction now approximating that of the blood. The observations support the view that within the body the autolysis of individual cells and of small tissue masses may take place under conditions of slight alkalinity.

AUTHOR'S SUMMARIES.

EXPERIMENTAL ELECTRIC SHOCK. R. W. I. URQUHART and E. CLARK NOBLE, J. Indust. Hyg. **11**:154, 1929.

When an alternating current of definite strength is passed directly through the base of the brain for a certain period of time, a condition of profound paralysis or block becomes established in the nerve centers. The presence of this block was demonstrated by experiments in which reflex effects normally functioning through these centers (respiratory, vagal, conjunctival) were found to be absent following the shock. It was further shown that, after a certain interval following break of the electric current, the paralysis or block is recovered from and the reflexes return, provided efficient artificial respiration is meanwhile applied, and provided there has been no charring of nerve structures. The institution of therapeutic means during this period of block (such as inhalation of air and oxygen mixtures, oxygen, carbon dioxide or intravenous injection of epinephrine) were of no avail, the application of efficient artificial respiration being the only factor responsible for shortening the block period.

An alternating current causes a similar condition of block in the centers of the lower portion of the spinal cord in decerebrated cats. This condition is manifested by the abolition of those reflexes that are dependent on the conductivity of that portion of the cord through which the current has passed. It was also found that following the passage of a relatively strong current through a nerve, a degree of block is established from which the nerve does not recover in a reasonable length of time.

C. G. WARNER.

THE MECHANISM OF OBSTRUCTIVE PULMONARY ATELECTASIS. C. M. VAN ALLEN and W. E. ADAMS, Surg. Gynec. Obst. **50**:385, 1930.

Quiet or suppressed respiration with bronchial obstruction does not lead to pulmonary atelectasis in the normal lung.

Straining respiration is essential to the production of obstructive pulmonary atelectasis in the normal lung.

Valvular obstruction produces atelectasis much more rapidly than does total obstruction, but there is no evidence that valvular obstruction occurs spontaneously in man.

Pent up bronchial air is probably lost from the lung by absorption by the blood stream.

Obstructive atelectasis develops centrifugally through the parenchyma of the lung.

Decreased intrapleural and intrabronchial pressures occur characteristically in obstructive pulmonary atelectasis.

AUTHORS' SUMMARY.

MICRO-INJECTION STUDIES OF CAPILLARY BLOOD PRESSURE IN HUMAN SKIN. EUGENE M. LANDIS, Heart **15**:209, 1930.

The micro-injection method for directly determining mean blood pressure in single capillaries has been modified to suit the skin at the base of the human finger-nail. Average blood pressure in the arteriolar limb is 32 mm. of mercury; at the end of the loop, 20 mm., and in the venous limb, 12 mm. The fall of blood pressure does not cease at the junction of the arterioles and capillaries but continues unbroken through the capillary loop. Average blood pressure in the arteriolar limb is above, and in the venous limb below, the osmotic pressure of the plasma proteins. These direct pressure readings in human capillaries are in agreement with Starling's hypothesis of fluid balance. When the hand is placed at various levels above the suprasternal notch, the arteriolar and venous capillary pressures remain almost constant, but with the hand below the suprasternal notch they increase by the increment of hydrostatic pressure. Venous congestion by a pneumatic cuff produces a rapid rise of capillary pressure, which reaches cuff pressure within from fifteen to forty-five seconds. Capillary pressure finally

exceeds cuff pressure by from 8 to 14 mm. of mercury. Hyperemia of the skin at the base of the nail due to heat is accompanied by a rise of capillary pressure to as much as 60 mm. of mercury in the arteriolar limb and to as much as 45 mm. in the venous limb of the capillary. In the histamine flare, arteriolar capillary pressure rises to between 32 and 50 mm. of mercury, and venous capillary pressure to between 27 and 39 mm. Local cooling of the skin produces first a fall in capillary pressure of from 6 to 11 mm. of mercury, and after five to eight minutes a secondary rise of from 2 to 14 mm. above the original normal pressure. When the skin is whealed by freezing, average capillary pressure rises to 49 mm. of mercury in the arteriolar limb and to 32 mm. in the venous limb. In the blister, average arteriolar capillary pressure is 41 mm. of mercury, and average venous capillary pressure 23 mm. of mercury. The direct micro-injection method is compared, from the point of view of its accuracy, to certain direct and indirect methods. The observations are discussed with reference to the mechanism of fluid balance under average conditions and during hyperemia.

AUTHOR'S SUMMARY.

RELATION OF THE PREEN GLAND (GLANDULA UROPYGIALIS) OF BIRDS TO RICKETS. H. C. HOU, Chinese J. Physiol. **3**:171, 1929.

Removal of the preen glands from adult birds produces in some (fowl and duck) a marked disturbance of the plumage and an impairment of general health and in others (pigeons) only a slight disturbance of the plumage. Removal of the preen glands from young rachitic or normal fowls produces permanent rickets in spite of subsequent normal feeding, environment and sunshine. Occlusion of the opening of the preen glands of ducks causes some disturbance of plumage and loss of weight. The possible relationship between the sebaceous secretion and the formation of the antirachitic vitamin is discussed.

TESTICULAR GRAFTS. M. GIANOTTI and G. BERTINI, Arch. ital. di anat. e istol. pat. **1**:797, 1930.

Homoplastic grafting of testicular tissue was carried out subcutaneously, preperitoneally and in the tunica vaginalis of guinea-pigs and dogs. After from five to forty-five days, necrosis of the testicular tissue took place. After the first week, connective tissue proliferation and active exudation were observed in the surrounding tissue, without a cellular proliferation in the seminiferous epithelium or in the intertubular connective tissue.

E. WEISS.

THE RELATION OF THE HORMONE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO THE TESTIS. M. BORST, Deutsche med. Wchnschr. **56**:1117, 1930.

This hormone injected into young mice less than 26 days old stimulates the growth and division of the cells of the germinal epithelium. The interstitial tissue of the testis also proliferates; and the seminal vesicles and prostate gland increase in size much more rapidly than in untreated control animals. In mice older than 26 days, the germinal epithelium does not react so readily, and large doses produce degenerative changes. The prostate gland and seminal vesicles, however, increase rapidly in size as in younger mice, and the interstitial tissue of the testes also proliferates markedly.

PAUL BRESLICH.

THE EFFECT OF HYPOPHYSIS HORMONE ON YOUNG MALE RATS. H. BALTERS, Deutsche med. Wchnschr. **56**:1382, 1930.

Hormone from the anterior lobe of the hypophysis stimulates the differentiation of the infantile cell elements lining the tubules of the testes of young rats to spermatogonia and spermatocytes. In more mature animals the stimulation is less marked, and large doses of the hormone cause degenerative changes of the

germinal epithelium. The hormone also causes a marked proliferation of the interstitial tissue of the testis and stimulates the growth of the prostate gland and seminal vesicles which are distinctly larger than these tissues in untreated control animals.

PAUL BRESLICH.

EXCESSIVE USE OF TOBACCO AND CORONARY SCLEROSIS. K. PLENGE, Deutsche med. Wchnschr. **56**:1947, 1930.

The postmortem examination of two men, 46 and 40 years old, who had died suddenly, disclosed marked sclerosis of the coronary arteries in one, and a recent coronary thrombosis in the other. In each instance, the aorta and its main branches were practically unchanged. Both men had smoked tobacco excessively. Microscopically, there were regions of necrosis and sclerosis of the media of the coronary arteries that resembled the changes produced experimentally in animals by chronic nicotine poisoning. Nicotine is said to cause a spasm of the coronary arteries which eventually results in anatomic changes.

PAUL BRESLICH.

ALIMENTARY CHOLESTEREMIA AND BLOOD SUGAR IN DIABETES. E. SORKIN and M. BATUSCHANSKAJA, Ztschr. f. d. ges. exper. Med. **74**:138, 1930.

Diabetic hypercholesteremia is not dependent on the blood sugar, during fasting, but is directly related to the degree of acidosis. By feeding olive oil, the blood sugar may be lowered and the blood cholesterol raised. Similar changes may occur in persons with diabetes without feeding fat. In the first instance, the source of the increased cholesterol in the blood is exogenous; in the second instance, endogenous. The lowering of the blood sugar may be due to the checking influence of fat on the thyroid gland.

PEARL ZEEK.

EXERCISE AND SWEAT GLANDS. A. N. KRESTOWNIKOFF, Ztschr. f. d. ges. exper. Med. **74**:200, 1930.

Observations made on runners showed that the more lactic acid excreted in sweat, the less albumin appeared in the urine. The suggestion is made that the sweat glands may protect the kidney tissue from the action of lactic acid.

PEARL ZEEK.

THE EFFECT OF VITAMIN D AND PARATHYROID HORMONE ON THE STORAGE OF CALCIUM. FERDINAND HOFF and ERNST HOMANN, Ztschr. f. d. ges. exper. Med. **74**:258, 1930.

Following the injection of 50 units of parathyroid hormone (parathormone) in cases of tetany, a biphasic reaction occurred: at first there was a rise in the blood calcium, a decrease in the alkali reserve and a lessening of the potassium-calcium quotient; a leukocytosis with myeloid tendencies occurred and sensitivity to electrical stimulation was decreased; the symptoms of tetany disappeared. In the second phase, there was a disappearance of all these vegetative regulatory phenomena in reverse order. Parathyroid hormone and vitamin D are apparently antagonistic in their action in some respects. But experiments showed that visceral calcification following the administration of vitamin D was not lessened but actually increased by the simultaneous administration of parathyroid hormone. At the same time there was decalcification of skeletal bone, at times so great as to lead to spontaneous fractures.

PEARL ZEEK.

THE DEPOSITION OF VITAL DYES IN THE LYMPH NODES. S. SAWELSOHN, Ztschr. f. d. ges. exper. Med. **74**:607, 1930.

Subcutaneously injected trypan blue and india ink are subsequently held partly by the subcutaneous tissues and partly by the regional lymph nodes. If a dye concentration of 1:10,000 is used, the deposition is in the histiocytes of the con-

nective tissues at the injection site, none being found in the regional lymph nodes two days after injection. If a concentration of 1:1,000 is used, the dye appears also within the lymph nodes. A concentration of 1:100 causes, in the same time interval, a deposition of dye in the reticulo-endothelium of the internal organs. Blocking of the lymph nodes with india ink several days previously, apparently has no effect on the fate of subsequent injections of trypan blue. Venous hyperemia in the extremity chosen for subsequent injections of dyes does not prevent deposition, either local or at distant sites, but complete blockage of the venous circulation is a real hindrance to the deposition of the dye in the regional lymph nodes and prevents its deposition in the internal organs.

PEARL ZEEK.

THE EFFECT OF TUBERCULOUS INFECTION ON METABOLISM. HANS FISCHER and EDWARD FROMMEL, Ztschr. f. d. ges. exper. Med. **74**:646, 1930.

In experimentally produced acute miliary tuberculosis, there occurs, during the incubation period, a definite increase in the consumption of oxygen, which cannot be attributed to fever. Likewise, during the manifest stage of the disease, the increased metabolism does not run parallel to the temperature. Various explanations are offered for this phenomenon.

PEARL ZEEK.

DEGENERATION OF THE TUBER CINEREUM AS A FACTOR IN THE DESTRUCTION OF THE CELLS OF THE UPPER SYMPATHETIC GANGLION. G. IWANOW, Ztschr. f. d. ges. exper. Med. **74**:773, 1930.

Experimental injury to the tuber cinereum was followed by degenerative changes in the superior cervical ganglion, beginning usually as a chromatolysis and homogeneous appearance of cytoplasm and nucleus, then a change in shape of the nucleus and finally complete disappearance of the nucleus. Changes were observed also in the neurofibrils.

PEARL ZEEK.

Pathologic Anatomy

SYPHILIS OF THE AORTA AND HEART. H. S. MARTLAND, Am. Heart J. **6**:1, 1930.

From a clinical and pathologic standpoint, I believe that we should regard syphilis of the aorta and heart as an acquired disease (congenital cases being infrequent) developing insidiously and showing symptoms years after the initial infection. It is possible to recognize clinically and to diagnose early aortitis, aortic regurgitation, narrowing of the coronary ostia, aneurysm or any combination of these lesions. Treatment and prognosis should be based mainly on such recognition. The myocardium in syphilis is frequently normal. When the aortic valve is involved, the main myocardial lesion is hypertrophy. Atrophy due to inanition is occasionally encountered. Specific lesions of the myocardium are infrequent and, when they occur, are so slight in extent as to be of little practical importance. It is safer and better to assume that the coronaries distal to the aortic wall are usually normal in pure, uncomplicated syphilis, and that coronary occlusions, anemic infarcts, necrosis of heart muscle, replacement fibrosis, aneurysms of ventricular walls and fibrous myocarditis are almost entirely due to coronary injury dependent on an arteriosclerotic process and have nothing to do with syphilis. That rheumatism and other infections may also produce forms of interstitial myocarditis is obvious. It appears that syphilis does not play an important rôle in the production of such lesions.

AUTHOR'S SUMMARY.

THE GROSS PATHOLOGY OF THE HEART IN CARDIOVASCULAR SYPHILIS. JAMES G. CARR, Am. Heart J. **6**:30, 1930.

Except for the predominant hypertrophy of the left ventricle, which resembles that of essential hypertension, the gross myocardial changes associated with syphilitic aortitis are not characteristic. The incidence of myocardial degeneration as a

result of syphilitic involvement of the coronary circuit is not great. The frequent occurrence of arteriosclerosis with syphilitic disease makes it difficult to separate these two factors as causes of coronary disease. Probably less than 10 per cent of the cases with aortic syphilis are associated with syphilitic coronary disease. In this series, involvement of the coronary orifices in the typical wrinkling of syphilitic aortitis was found only ten times, an incidence of 8.4 per cent. Aortic insufficiency is found in about 20 per cent of the hearts associated with syphilitic aortitis. It is the lesion most easily recognized and is most likely to be present in the advanced cases. In this series, it occurred in 19, or 37.2 per cent, of the hearts weighing over 450 Gm. Hypertrophy of the heart is a significant index of the degree of cardiac involvement in cardiovascular syphilis. This sign is absent in the latent stage of the disease, but becomes increasingly important as signs of cardiac disease appear. In a group of forty-four persons in whom autopsy showed definite cardiac enlargement of various degrees up to a maximum of 50 per cent, twenty-one died of intercurrent disease, and fifteen of these had not had a diagnosis of cardiac disease. Some of these presented symptoms of acute disease so marked as to cloud the picture, but others did not. Both aortic regurgitation and hypertension were infrequent in this group. The presence of an unexplained or "idiopathic" cardiac hypertrophy in persons of middle life may well excite the suspicion of syphilis. The two important causes of cardiac hypertrophy are aortic regurgitation and hypertension, the latter of which is a common occurrence in this type of case. There is a significant incidence of contracted kidney with advanced stages of cardiovascular syphilis. In this series, aneurysm was found more frequently in the cases characterized by relatively minor cardiac symptoms. These results seem to illustrate the frequency with which aneurysm may be present without involving the heart or causing symptoms of cardiac disease.

AUTHOR'S SUMMARY.

THE LOCALIZATION OF THE LUETIC VIRUS IN THE AORTA. J. W. MCMEANS, Am. Heart J. **6**:42, 1930.

It is our belief that in syphilitic aortitis the intima is involved primarily by direct infection from the blood stream. It may also be involved from the adventitia through the vasa vasorum. Histologically, the lesions are the same. Undoubtedly, the most serious lesions produced by syphilis in the aorta and heart are those of syphilitic aortic endocarditis with regurgitation and occlusion of the coronary orifices. This is intimal disease. Therefore, it would appear that syphilitic intimal disease of the aorta is more important clinically than syphilitic medial disease.

AUTHOR'S SUMMARY.

HYPERPLASIA OF THE CORPUS ADIPOSUM BUCCAE (SUCKING PAD). FRANK C. NEFF and JOHN A. BILLINGSLEY, Am. J. Dis. Child. **40**:813, 1930.

We have been able to find the record of a unilateral hyperplasia of the corpus adiposum malae in a 15 year old boy and a few cases of lipoma limited to one side in children past infancy. We have been unable to learn of any report in which mention is made of bilateral pathologic enlargement confined to the corpus adiposum buccae in the newly born child. Scammon, as a result of his research on the development and fine structure of the sucking pads, found that at birth the pad is a structure particularly prominent in the well nourished child. In fetal life the growth in the first five months is principally due to increase in the number of fat lobules. In the later fetal months, the fat body grows because of the forming of new fat cells and the increase in size of the individual fat cells. Scammon stated that new fat cells stop forming usually by the end of the seventh fetal month, occasionally not until the last month. In the case here reported the infant was not robust at first, but was small and premature, and possibly was affected by the toxic state of the parturient mother. The cheeks were not wasted. It is possible that the fat pads continued to grow for the first ten or twelve days after birth, and at a rapid rate after feeding and the normal influences of growth were established. As a more

plausible explanation, the finding of a mild inflammatory reaction in the biopsy material and the subsequent rather rapid decrease in the size of the remaining fat pad would suggest that the enlargement of these bodies may have been hyperplastic, due to a toxic influence.

AUTHORS' SUMMARY.

MEDIASTINAL TERATOMA IN AN INFANT. HERBERT B. WILCOX and MARTHA WOLLSTEIN, Am. J. Dis. Child. **41**:89, 1931.

A solid mediastinal teratoma occurring in a male infant, aged 6 months, and giving symptoms over a period of three months, is described, with the microscopic content of tissues from the three embryonal layers.

AUTHORS' SUMMARY.

SUBACUTE BACTERIAL ENDARTERITIS OF PULMONARY ARTERY ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS AND PULMONIC STENOSIS. HARRY GORDON and DAVID PERLA, Am. J. Dis. Child. **41**:98, 1931.

An instance is reported of subacute bacterial endarteritis (*Streptococcus viridans*) of the pulmonary artery associated with a patent ductus arteriosus and congenital pulmonary stenosis. None of the valves was involved. The relationship of congenital defect to bacterial inflammation is discussed.

AUTHORS' SUMMARY.

JUVENILE EMBOLIC GANGRENE OF AN UPPER EXTREMITY. JOHN DORSEY CRAIG and WALDEN E. MUNS, Am. J. Dis. Child. **41**:126, 1931.

A case of aortic stenosis of rheumatic origin with an accompanying embolic gangrene of the right hand in a child is here reported because of its clinical interest and rarity.

AUTHORS' SUMMARY.

TUBULAR NEPHRITIS (NEPHROSIS). S. BURT WOLBACH and KENNETH D. BLACKFAN, Am. J. M. Sc. **180**:453, 1930.

We believe that the eight cases here presented, because of the clinical and pathologic features common to them all, are representative of a disease entity in childhood. This belief implies a common etiology or pathogenesis for the series. The pathologic changes in the kidneys afford no premises for the explanation of the important physiologic disturbances, and therefore we do not believe that the primary effect of the etiologic agent is on the kidneys or that the important manifestations of the disease are consequences of injury specific to the kidneys. The histologically demonstrable damage to the kidneys was found in the tubules. The glomeruli showed only lesions accountable for either by the terminal infection or severe degeneration of the tubules of the same units. In general, the glomeruli were without lesions. A conclusion regarding the rôle of the thyroid gland in this disease is not possible. The lesion in the thyroid gland is probably a manifestation of functional exhaustion and therefore probably is neither cause nor direct consequence of the damage to the kidney. The pathologic changes in the liver, slight atrophy and degeneration of the hepatic cells, may also be interpreted as effects of overtaxed functional activity consequent to the loss of proteins from the blood. While offering no substitute, we believe that any name implying a renal origin, such as nephrosis or tubular nephritis, is not appropriate to this disease.

AUTHORS' SUMMARY.

MITOSIS IN MYELOBLASTS IN PERIPHERAL BLOOD. WILLIAM A. GROAT, Am. J. M. Sc. **180**:607, 1930.

Photomicrographs of a series of leukoblastic cells in mitotic division are shown. These cells from the circulating blood of a patient with acute myeloblastic leukemia form a complete series of mitotic figures from early prophase through metaphase

and anaphase to latest telephase. The angle that the chromosomes bear to the spindle can be measured approximately in these photomicrographs and is found to be close to 70 degrees, agreeing with the goniometric measurements made by Ellermann of myeloblasts in tissue sections. Mitotic division in leukemic cells in peripheral blood is added evidence of a possible relationship between leukemia and malignant growth.

AUTHOR'S SUMMARY.

ACUTE INTERSTITIAL PANCREATITIS IN TWO CASES OF DIABETIC COMA. ALVIN G. FOORD and BYRON D. BOWEN, Am. J. M. Sc. **180**:676, 1930.

Two fatal fulminating cases of diabetic coma in young adults have been reported with the observations at necropsy. The chief pathologic change in each of these cases was acute diffuse interstitial pancreatitis, which was probably a factor in the precipitation of coma. Examination of the literature shows only one similar case (Warren) and another (Gibb and Logan) associated with an infected hand. In our two cases no source of the infection could be determined. In one of our cases there was histologic evidence of a high degree of disturbance in lipid metabolism as manifested by a huge liver that showed extreme fatty metamorphosis, by the deposit of lipid substance in the abdominal lymph nodes, spleen and kidney, and by lipemia. It is extremely probable that in this case the diabetes had not been fully under control for some time, as the patient had not previously seen a physician in about three years and was an unmanageable patient, as we know from past experience with him.

AUTHORS' SUMMARY.

GASTRIC HEMORRHAGE DUE TO FAMILIAL TELANGIECTASIS. L. NAPOLEON BOSTON, Am. J. M. Sc. **180**:798, 1930.

Familial telangiectasis is the etiologic factor in a definite class of hemorrhages, which take place in the presence of normal physiologic responses by both the capillary and the venous blood. Recurrent gastric hemorrhages were experienced during early life by each of the three patients whose cases were studied; and attacks of hemorrhage were often accompanied by brief periods of syncope. Judged by the small number of reports of cases, familial telangiectasis does not shorten the span of life or inhibit development. Familial gastric hemorrhage has been observed in persons who have also experienced recurrent attacks of hemorrhage from other mucous surfaces. The vascular defects common to the familial condition characterized by hemorrhages from the mucous membranes are to be found among other members of the same family and in their near relatives. The tendency to familial hemorrhage is transmitted by both the maternal and the paternal parent to the offspring.

AUTHOR'S SUMMARY.

TROPICAL SPRUE. ITS DIFFERENTIATION FROM PERNICIOUS ANEMIA BY THE ARNETH COUNT. JAMES D. TYNER, Am. J. Trop. Med. **10**:435, 1930.

The average Arneth index of ten cases of pernicious anemia was 32.45. The average Arneth index of seventeen of twenty cases of tropical sprue was about normal, or 62.1. The Arneth count may be of aid in the differential diagnosis of tropical sprue and pernicious anemia.

AUTHOR'S SUMMARY.

LEUKEMIC CHANGES OF THE GASTRO-INTESTINAL TRACT. W. SCLAIR BOIKAN, Arch. Int. Med. **47**:42, 1931.

Fourteen cases of leukemia, eleven myelogenous and three lymphatic, were studied with reference to the gastro-intestinal involvement. Nonspecific changes were found in nine cases of acute myelogenous leukemia, consisting of hemorrhages, ulceration and secondary inflammatory processes. In two cases (acute myelogenous leukemia) there were no changes. Specific changes were found in two cases of

acute myelosis, consisting of an infiltration of the appendix and an infiltration of Peyer's patches, respectively. Specific changes were found in one case of chronic lymphatic leukemia: the stomach was enormously enlarged, with huge convolutions on the inner surface, giving it a brainlike appearance, and the intestines were beset with plaques and polyp-like infiltrations. In reviewing the literature, no similar case was discovered. The case was found, however, to parallel exactly those described as aleukemic lymphadenosis or pseudoleukemic gastro-intestinalis. From these facts it is concluded that the aleukemic and leukocythemic leukemias are fundamentally identical. In further support of this conclusion, a last case is described in which an aleukemic lymphadenosis terminated as an acute leukocythemic lymphadenosis. The symptoms in leukemia gastro-intestinalis are briefly discussed, and their importance is emphasized.

AUTHOR'S SUMMARY.

TUMOR OF THE FILUM TERMINALE. E. SACHS, D. K. ROSE and A. KAPLAN, Arch. Neurol. & Psychiat. **24**:1133, 1930.

As only three cases of tumor of the filum terminale are on record (those of Lachman, Gowers and Spiller), the two cases reported here are of interest. In the first case the essential complaints were difficulty in urination followed by acute retention, a "neurogenic" bladder, saddle-like anesthesia (corresponding to the third, fourth and fifth sacral segments of the skin), hyperactive ankle and knee jerks, ankle clonus, a Babinski sign on the left and an Oppenheim sign bilaterally. The pressure of the spinal fluid, which was 90 mm., rose, after bilateral jugular compression for ten seconds, to 170 mm.; the result of the Pandy test was 2 plus; otherwise the spinal fluid was normal. Though tumor of the spinal cord was diagnosed, its location could not be determined, even with the injection of iodized poppy seed oil 40 per cent; this dropped to the bottom of the canal. Operation revealed an encapsulated tumor, 4 by 1.5 cm., containing several cysts, attached at one end to the spinal cord with which it was fused and at the other end to a thin fibrous cord. The microscopic diagnosis was hemangio-endothelioma. The patient recovered completely.

In the second case, the initial symptoms were progressive atrophy and weakness in the lower portions of both legs for several years, followed by pain and soreness and dysuria; the ankle jerks were absent; sensory disturbances were present in the areas of the fourth and fifth sacral segments and hypesthesia to pin pricks was detected on the posterior surface of the knee downward to the lower portion of the gastrocnemius muscle. An Oppenheim sign was present on the left and a normal ankle jerk on the right. The rectal sphincter was relaxed. Spinal puncture showed no evidence of block. Operation disclosed a tumor, 3.5 by 2 by 1 cm., of the filum terminale; it weighed 2 Gm. (hemangio-endothelioma). Its removal was followed by marked improvement in the bladder and some improvement in the legs. Studies of cases of disease of the filum terminale may help clear up the physiology of micturition, which is not fully understood.

GEORGE B. HASSIN.

HYDROCEPHALUS. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **24**:1164, 1930.

The study of twelve cases of hydrocephalus of so-called communicating type in which the obstruction is elsewhere than in the ventricles, revealed, aside from the distention of the latter by excessive amounts of fluid, also dilatation of the subarachnoid spaces, mainly over the convexity of the brain, and of the cerebral tissue spaces. The condition was one of general hydrops involving the brain and the intracerebral (ventricles), as well as the extracerebral (subarachnoid) cavities. In all the cases, the choroid plexuses, which are supposed to produce the excessive amounts of the fluid in hydrocephalus, were atrophied or sclerosed or buried within the ventricular tissue. The pacchionian bodies, which according to the popular conception drain the spinal fluid, were excessively developed and not shrunk as they should have been if they drain the spinal fluid. The perineural spaces along the cranial nerves were infiltrated and some basilar cisterns, especially the chiasmatic,

appeared obliterated by the protruded floor of the third ventricle. In general, there were infiltrations with hematogenous elements, hyperplasia of connective tissue and in one instance, in an infant, ossification of the dura, in the ventricles, subarachnoid spaces, choroid plexuses, perineural spaces of the cranial nerves, the meninges and the cerebral tissue themselves. Of these the changes in the ventricles, cerebral parenchyma, arachnoid villi and pacchionian bodies were secondary to those in the meninges, the subarachnoid and the perineural spaces of the cranial nerves. The result of the latter changes was interference with the discharge of the cerebrospinal fluid which normally occurs into the ventricles and the subarachoid spaces from the cerebral tissues by way of the Virchow-Robin spaces. As the choroid plexuses were severely damaged in all the cases, they could not be responsible for the excessive accumulation of the fluids. They are thus not the secretory, but most likely, as other pathologic facts indicate, the excretory, organs. They hold back the harmful products of the tissue fluids, rendering them harmless and absorbable. It also follows that the pacchionian bodies do not serve the purpose of absorption of the cerebrospinal fluid, which is absorbed exclusively by way of the perineural spaces of the cranial nerves.

AUTHOR'S ABSTRACT.

SCHILDER'S ENCEPHALITIS PERIAXIALIS DIFFUSA. M. M. CANAVAN, Arch. Neurol. & Psychiat. **25**:299, 1931.

Canavan's patient, a rather poorly nourished child, with a history of nasal discharge and a swollen ear drum was observed continuously from the age of 10 weeks to that of 16½ months, when the child died. The most prominent symptoms were increased size of the head, which suggested hydrocephalus, nystagmus, vomiting and mental deficiency; "it was questionable whether the child saw objects"; optic atrophy (beginning) was noticed. At one examination (at the age of 16 months) strabismus and Kernig's sign were present, with increased knee jerks. Necropsy revealed bulging of one hemisphere, a firm cortex (after hardening in a solution of formaldehyde), and pink, soft, retractile white matter "resembling mucoid degeneration" especially in the posterior portion of the brain; the whole cerebellum, though it had been in formaldehyde for almost three months, was soft to the touch. Microscopic examination showed lacy edema, especially of the cerebellum, with traces of glial cells fairly well preserved, absence of fat, traces of which were present only in the walls of the blood vessels, and subcortical loss of myelin. The weight of the brain was 1,890 Gm.

GEORGE B. HASSIN.

THE CELLS OF THE SPINAL ARACHNOID IN PATHOLOGIC CONDITIONS. I. B. DIAMOND, Arch. Neurol. & Psychiat. **25**:373, 1931.

Diamond studied the condition of the arachnoid cells, also known as mesothelial cells or membrane cells of Key and Retzius, in tabes, taboparesis, multiple sclerosis, multiple myeloma of the vertebrae, myelomalacia, subacute combined degeneration of the cord, spinal syphilis, streptococcus infection, tetanus, neurinoma, uremia, Pott's disease, carcinoma of the mediastinum, hemiplegia and in normal conditions. The arachnoid at various levels of the spinal cord was gently stripped from the pia, clipped with scissors and stained by various methods, especially the hematoxylin staining method of Ehrlich. In all the cases the arachnoid cells appeared proliferated and often showed mitotic figures and cluster formation. The clusters were present largely on the posterolateral surfaces of the cord and on the posterior roots. Over the anterior aspect of the cord they were less in evidence. Of the pathologic conditions, tabes showed abundant nests, which were also much denser than in other conditions. Contrasting the changes seen in arachnoid cells in tabes with those seen in other conditions, such as subacute combined degeneration of the cord, multiple sclerosis, myelomalacia, etc., Diamond came to the conclusion that they differ somewhat, depending most likely on the spinal fluid. Exposed to the latter, the arachnoid cells react differently according to the sub-

stances in the fluid. As the spinal fluid in tabes differs, for instance, from that in multiple sclerosis, the reaction also differs. This is fully borne out by the histologic changes. In general, the cell changes are simple swelling, active proliferation, formation of macrophages, focal hyperplasia with formation of cell clusters, a diffuse infiltration with a tendency to syncytial formation and frequent regressive changes, such as calification.

GEORGE B. HASSIN.

TUBERCLE-LIKE STRUCTURES IN HUMAN GOITERS. R. H. JAFFÉ, Arch. Surg. **21**:717, 1930.

Epithelioid, giant cell, tubercle-like structures are found occasionally in both diffuse hyperplasia and nodular goiters. They have been considered as tubercles. On the basis of 4 cases in 300 specimens, the author believes that these are not tubercles. No caseation or tubercle bacilli were found in the tissues in these 4 cases, and transformation of follicles into nodules could be demonstrated, while the epithelioid-like cells and giant cells could be traced to the follicular epithelium. The author believes that these pseudotuberculous formations are the result of involutionary changes in old and newly formed follicles.

N. ENZER.

COMPLETE OCCLUSION OF THE SUPERIOR VENA CAVA BY PRIMARY CARCINOMA OF THE LUNG. A. L. BROWN, Arch. Surg. **21**:959, 1930.

The author gives a report of a case of primary peribronchial carcinoma in a man 65 years of age, with complete obstruction of the superior vena cava by compression and subsequent thrombosis.

N. ENZER.

CONGENITAL SYPHILIS OF ADRENAL. G. L. FITE, Bull. Johns Hopkins Hosp. **48**:1, 1931.

The adrenals in 250 cases of congenital syphilis were studied. No instance of macroscopic gumma was noted. When spirochetes were found in congenital syphilis they were practically always demonstrable in the adrenal, without, however, being associated with any constant alteration in structure. Foci of blood-forming cells may be rather more striking than normally in the adrenal, owing apparently to prematurity, anemia, or both. Necrosis, with or without inflammatory changes, was present in the adrenal in some of the cases, but probably the most frequent and characteristic lesion of the adrenal is increase in the connective tissue of the capsule, frequently associated with active inflammatory changes.

HISTOLOGIC AND TOPOGRAPHIC STUDY OF CHRONIC GASTRITIS. K. HILLENBRAND, Beitr. z. path. Anat. u. z. allg. Path. **85**:1, 1930.

From Aschoff's institute comes this further contribution to the pathology of the gastric mucosa. Hillenbrand investigated the lesions of chronic gastritis with regard to their frequency, histologic character and topographic distribution. The stomach was removed as soon after death as possible and fixed in formaldehyde solution. Since previous investigations had established that chronic gastritis is most frequent after the middle period of life, the stomachs of persons over 35 years of age were examined. Twenty-one stomachs were found to be free of autolytic changes and suitable for study. Two each were from the fourth, fifth and ninth decades, four from the sixth decade, five from the seventh decade, and six from the eighth decade. Seven were from women and fourteen from men. The histologic alterations accepted as evidence of chronic gastritis were: atrophy of the mucosa; increase in the number and size of lymphoid follicles and diffuse lymphocytic infiltration; the presence in the pylorus or in the fundus of mucosa of the type found in the small intestine or of pyloric glands in the fundus, and

hypertrophic thickening of the muscularis mucosae. For the description of the interesting technical procedure by means of which it was possible to examine histologically with a reasonable degree of completeness the entire gastric mucosa, the reader is referred to the original. Of the twenty-one stomachs that were examined, all but eight revealed the presence of the intestinal mucosa. Atrophic changes were present in four of the remaining eight stomachs. Chronic gastritis is more common in males than in females, since four of the seven stomachs of women failed to reveal chronic changes, whereas only four of seventeen stomachs of men were free from such changes. The transformation of gastric mucosa into intestinal mucosa may occur in localized areas or may be more diffuse or widespread. The localized transformation is held to be the result of metaplasia in the regenerative healing of acute inflammatory erosions of the mucosa, whereas the more diffuse process results from atrophy of the mucosa. Hillenbrand attempts to correlate the alterations noted with the pathologic physiology of gastric secretion. He concludes that chronic gastritis of the entire mucosa which leads to disappearance of glands from the fundus results in true achylia, which is not influenced by histamine. Chronic gastritis limited to the pylorus leads to an achylia that is overcome by histamine.

O. T. SCHULTZ.

HYALINE GLOMERULI IN THE KIDNEYS OF NEW-BORN INFANTS AND NURSLINGS. K. SCHULZ, Beitr. z. path. Anat. u. z. allg. Path. **85**:33, 1930.

Herxheimer noted the presence of hyaline glomeruli in the kidneys of 80 per cent of new-born infants and nurslings examined by him and ascribed such glomeruli to maldevelopment and regression of incompletely developed glomeruli. Schwarz, in a later contribution on the subject, detected hyaline glomeruli in the kidneys of 80 per cent of nurslings over 3 weeks of age and in only 30 per cent of infants under this age. The greater frequency of hyalinization of the glomeruli after 3 weeks of age and the frequent association of the process with infiltrative and degenerative lesions of the kidney led Schwarz to conclude that hyaline glomeruli are the end-stage of an inflammatory process, brought about by postnatal infection or prenatal or postnatal toxic damage. Schulz, working in Herxheimer's laboratory, made a microscopic study of the kidneys of fifty-two fetuses and very young infants. His material consisted of eleven fetuses less than 48 cm. long, fifteen new-born infants, eight nurslings up to 1 month of age, and eighteen nurslings over 1 month old. Hyaline glomeruli were seen in 90.3 per cent. The five cases in which such glomeruli were not found concerned fetuses less than 35 cm. long. The most common localization of hyaline glomeruli was in the middle and deep zones of the cortex. They were as a rule present in otherwise normal kidneys, although occasionally associated with focal subacute inflammatory lesions in the kidneys of the older infants. Although focal inflammation may at times lead to hyalinization of isolated glomeruli, the occurrence of the process in the kidneys of fetuses and in kidneys that reveal no degenerative or inflammatory reactions leads Schulz to conclude that hyalinization of isolated glomeruli of infants is usually the result of maldevelopment.

O. T. SCHULTZ.

Immunology

THE EFFECT OF DISEASES OTHER THAN DIPHTHERIA ON THE SCHICK TEST. BERNICE EDDY and A. GRAEME MITCHELL, Am. J. Dis. Child. **40**:985, 1930.

Diseases such as measles and scarlet fever do not affect the reactions to the Schick test; that is, during the acute febrile and the convalescent stages of these diseases, there is no difference in the skin reaction to diphtheria toxin.

AUTHORS' SUMMARY.

THE EFFECT OF DISEASES OTHER THAN SCARLET FEVER ON THE DICK TEST. BERNICE EDDY and A. GRAEME MITCHELL, Am. J. Dis. Child. **40**:988, 1930.

Apparently, certain diseases during their acute febrile stages occasionally cause a positive Dick reaction to become negative. This does not occur regularly, and the evidence so far accumulated in the literature indicates that measles is especially apt to cause this depression in the skin reaction to scarlet fever toxin. There may be a delay in the skin reaction to injections of scarlet fever toxin so that erythema occurs at the site later than twenty-four hours after its injection. Whether this is a pseudoreaction or just what it signifies we are not prepared to state. In about 90 per cent of the patients, the skin reaction to a heat-killed suspension of scarlet fever streptococci was similar to that obtained with scarlet fever toxin. Great variation, which was probably not due to errors in the technic of injection, was encountered in the skin reaction to scarlet fever toxin in the acute and convalescent stages of scarlet fever. Some patients had positive reactions throughout the entire course of the disease and some had negative ones; others had reactions which varied from positive to negative or from negative to positive. About 30 per cent of the patients had positive reactions thirty-one days or longer after the onset of scarlet fever.

AUTHORS' SUMMARY.

RAPIDITY OF IMMUNIZATION WITH DIPHTHERIA TOXOID. M. COOPERSTOCK and G. F. WEINFELD, Am. J. Dis. Child. **40**:1035, 1930.

Observations are recorded on the rapidity of immunization with the routine employment of two injections of diphtheria toxoid, 1 cc. each, with an interval of three weeks between injections. Of a group of fifty subjects retested three weeks after the second injection, twenty-nine, or 58 per cent, were found to give negative reactions to the Schick test. In a second group, consisting of forty-four subjects, it was found that thirty-five, or 79.5 per cent, gave negative reactions nine weeks after the second injection. In a third group of sixty-five subjects, sixty, or 92.3 per cent, showed a negative reaction from sixteen to twenty-two weeks after the second injection. Our results and those reported by others suggest that the employment of two injections of 1 cc. each, three weeks apart, is, for practical purposes, an adequate routine procedure in diphtheria vaccination. It is pointed out that spacing the injections too closely may delay immunity.

AUTHORS' SUMMARY.

THE TRYPANOCIDAL ACTION OF SPECIFIC ANTISERUMS ON TRYPANOSOMA LEWISI IN VIVO. FRANCES A. COVENTRY, Am. J. Hyg. **12**:366, 1930.

A passively transferable trypanocidal substance was demonstrated in serum obtained from rats during the course of uninfluenced infections with *Trypanosoma lewisi*. When the serum was tested in vivo against *T. lewisi* which had just appeared in the blood but had not yet undergone a number crisis, the trypanocidal power was manifested by a decrease in numbers or by the complete disappearance of the trypanosomes within from one to five hours after the injection of the serum. The presence of a trypanocidal substance in the serum during the course of infection is probably correlated with the occurrence of the first number crisis which occurs in uninfluenced infections with *T. lewisi* from about the sixth to the tenth day of infection. Serum obtained from rats shortly after the end of an uninfluenced infection exhibited a similar trypanocidal action when tested in the same way. Such serum was trypanocidal to trypanosomes tested either before or after the first number crisis. Serum tended to lose its curative power within a few weeks after the termination of infection. When serum obtained during or soon after the end of infection was given in graded doses to a series of rats, in certain series recurring zones of complete or partial action and of inaction tended to occur, i. e., the serum caused the complete disappearance or the diminution in number of

trypanosomes in certain doses of a series, was ineffective in slightly higher doses, was effective in still higher ones, and so on. The zonal phenomenon appeared to depend on the number of trypanosomes present in the rats at the time the doses of serum were administered: (*a*) when there were very few trypanosomes (from 1 to 20 per field), the serum tended to be effective in all doses; (*b*) when there were slightly more numerous trypanosomes (from 20 to 40 per field), the serum tended to show the zonal phenomenon, and (*c*) when there were very numerous trypanosomes (approximately 50 per field) the serum tended to be ineffective. The curative effect was more marked after the intravenous injection of the serum, but curative and zonal action followed either intravenous or intraperitoneal injection. Inactivation did not decrease the curative power of the serum. Moreover, the zonal phenomenon was independent of inactivation. Serum from rats and rabbits hyperimmunized against *T. lewisi* by repeated injections of the living parasites exhibited similar curative and zonal action.

AUTHOR'S SUMMARY.

THE RELATION IN CHILDREN OF ERYTHEMA NODOSUM TO TUBERCULOSIS. LLOYD B. DICKEY, Am. J. M. Sc. **180**:489, 1930.

Erythema nodosum may occur in nontuberculous persons or in those infected with the tubercle bacillus. The great majority of cases of erythema nodosum in children are associated with a tuberculous infection, and most of the infections are initial and recent. Most children who have erythema nodosum exhibit marked hypersensitiveness to tuberculin given intracutaneously. In addition to the tuberculous infection, other conditions may be present which possibly influence hypersensitiveness to tuberculin. In many cases of erythema nodosum in children epituberculous lesions in the pulmonary parenchyma can be demonstrated by roentgenograms of the chest. In none of the patients observed in the series reported was a very active tuberculous lesion of the lung known to develop. The lesions of erythema nodosum, the epituberculous lesions and the positive skin reactions to tuberculin are similar histologically. As erythema nodosum in children is usually associated with early tuberculous infections, proper treatment for the latter condition gives a favorable prognosis as far as tuberculosis is concerned.

AUTHOR'S SUMMARY.

TISSUE-IMMUNITY. P. R. CANNON and G. A. PACHECO, Am. J. Path. **6**:749, 1930.

This paper describes histopathologic studies of the skin and subcutaneous tissues of the abdominal wall of normal guinea-pigs and of those previously immunized by intracutaneous injections of a staphylococcus vaccine, which were infected by the intracutaneous injection of a live virulent culture of *Staphylococcus aureus*. The inflammatory responses were markedly different in the two groups. In the normal animals the inflammation was characterized mainly by an infiltration of polymorphonuclear leukocytes which actively phagocytosed the micro-organisms. In spite of this, the staphylococci showed no tendency to localize, but disseminated throughout the subcutaneous tissues in the form of a cellulitis. In the previously immunized animals, however, the staphylococci tended to remain localized near the site of inoculation where they were seen agglomerated in bacterial masses of various sizes, presenting the picture of a genuine agglutination in vivo. Coincidently, the infiltration of cells of inflammation led to further localization of the micro-organisms so that only a localized area of necrosis resulted. The previous immunization by intracutaneous injections of the staphylococcus vaccine was followed by a marked thickening of the subreticular layer of the subcutis, due mainly to the activation or production of increased numbers of tissue macrophages. Evidence is presented that many of these are derived from agranulocytes of the blood. These macrophages were actively phagocytic for the live staphylococci and furnished an effective barrier against extension of the infection. The immunity secured by these procedures is predominantly cellular in type, with the tissue-

macrophages playing the dominant part, owing to increased numbers and also probably to increased metabolic activity. In addition, localization of the microorganisms by the action of agglutinating or opsonizing antibodies is suggested as of primary importance in preventing the dissemination of the infectious agent. The combination of humoral and cellular mechanisms insures an adequate resistance against the bacterial invaders.

AUTHORS' SUMMARY.

ANTIBODY FORMATION IN KALA-AZAR. H. L. CHUNG and HOBART A. REIMANN, Arch. Int. Med. **46**:782, 1930.

In patients with kala-azar and leukemia the immune response to typhoid vaccination shows a marked depression. After recovery from kala-azar, agglutinins are again formed normally.

AUTHORS' SUMMARY.

SPECIFIC POLYSACCHARIDES FROM FUNGI. H. D. KESTEN, D. H. COOK, E. MOTT and J. W. JOBLING, J. Exper. Med. **52**:813, 1930.

From each of five yeastlike fungi and a *Trichophyton* a fraction which appears to be essentially a polysaccharide has been prepared. Tested by direct precipitation against the corresponding antiserums, the polysaccharides from the yeastlike fungi exhibit only partial specificity. Cross-precipitation reactions are frequent. By absorption of precipitin on the intact mycotic bodies, however, a relatively high degree of specific precipitability can be demonstrated for the polysaccharides.

AUTHORS' SUMMARY.

CHEMICAL AND IMMUNOLOGICAL PROPERTIES OF A SPECIES-SPECIFIC CARBOHYDRATE OF PNEUMOCOCCI. W. S. TILLETT, W. F. GOEBEL and O. T. AVERY, J. Exper. Med. **52**:895, 1930.

Pneumococci contain a nonprotein constituent, which, on the basis of its chemical and immunologic properties, appears to be a carbohydrate distinct from the type-specific carbohydrate and common to the species.

AUTHORS' SUMMARY.

TYPE-SPECIFIC PROTECTIVE ANTIBODY IN ANTIPNEUMOCOCCUS SERUM NOT NEUTRALIZED BY HOMOLOGOUS SPECIFIC SOLUBLE SUBSTANCE. A. B. SABIN, J. Exper. Med. **53**:93, 1931.

The mutual relationship of the anticarbohydrate precipitins and of the protective action in antipneumococcus serums to the soluble specific substance was investigated. The assumption is made that there exists in antipneumococcus serum, a type-specific, protective antibody which is distinct from the anticarbohydrate precipitins and is not neutralized by the soluble specific substance. This assumption is based on the following observations in experiments which were conducted primarily with type 1 antipneumococcus horse serum. There was a lack of proportion between the quantity of specific soluble substance added and the amount of anticarbohydrate precipitin and protective action neutralized. The protective capacity of specific precipitates (specific soluble substance-precipitin complex) is accounted for on the basis of a liberation of nonspecifically adsorbed protective antibody. Specific soluble substance only partially neutralizes the protective action of antipneumococcus serum in vivo. The type-specific protective antibody remains in antipneumococcus serum after complete precipitation of the anticarbohydrate precipitins This residual type-specific protective antibody is not neutralized by additional specific soluble substance nor by absorption with heterologous pneumococci; it is definitely absorbed by the homologous pneumococci.

AUTHOR'S SUMMARY.

THE EFFECT OF ALEXIN ON MIXTURES OF ROUS SARCOMA VIRUS AND ANTIVIRUS. J. HOWARD MUELLER, J. Immunol. **20**:17, 1931.

Antibodies against the agent of the Rous fowl sarcoma were produced in geese, ducks and rabbits by injections of suspensions of the sarcoma, and in chickens by injections of similar suspensions which had been heated. The viricidal effect is enhanced by an hour's incubation at 37 C. with fresh, unheated guinea-pig complement; heating at 50 C. for fifteen minutes destroys this effect.

AUTHOR'S SUMMARY.

THE ACTION OF FORMALDEHYDE ON DIPHTHERIA TOXIN. W. E. BUNNEY, J. Immunol. **20**:47, 1931.

Evidence is offered which indicates that the formation of toxoid is not the result of the direct action of free formaldehyde on the diphtheria toxin. Results are obtained which suggest that the formation of toxoid by the action of formaldehyde on diphtheria toxin may depend on a compound resulting from the reaction between formaldehyde and the amino group in an amino-acid. A possible method for making acceptable toxoid from lower grade diphtheria toxins is suggested.

AUTHOR'S SUMMARY.

SEROLOGIC STUDIES ON THE PROTEINS FOUND IN CASEIN. D. C. CARPENTER and G. J. HUCKER, J. Infect. Dis. **47**:435, 1930.

It has been shown that the proteins occurring in crude casein and having molecular weights, respectively, of 98,000, 188,000 and 375,000 are clearly distinguishable from one another by serologic reactions. The production of coctoprecipitin specific for a heated antigen and the distinguishing of it from unheated antigen has been recorded. The alcohol-soluble protein of Osborne and Wakeman does not appear to be the same as the acid-alcohol soluble protein having a molecular weight of 375,000.

AUTHORS' SUMMARY.

ERROR IN GROUPING FROM CONTAMINATION WITH "MUSTARD BACILLUS"—TRANSFUSION OF INCOMPATIBLE BLOOD. E. F. GROVE and M. J. CRUM, J. Lab. & Clin. Med. **16**:259, 1930.

Owing to contamination of a serum with a "mustard bacillus," which produces a nonspecific power to clump human corpuscles of all groups, a patient of group O was given a transfusion of 300 cc. of group B blood. Fortunately, no harmful reaction developed, probably because the agglutinin did not clump B corpuscles at the temperature of the body.

THE TITRATION OF SCARLATINAL ANTITOXIN BY SKIN TEST IN CHINCHILLA RABBITS. F. H. FRASER and H. PLUMMER, Brit. J. Exper. Path. **11**: 291, 1930.

A series of dilutions was made of each antitoxin to be tested, and 2 cc. of each dilution was mixed with an equal amount of toxin dilution, incubated at 37 C. for one hour and injected into rabbits and human beings intradermally. A comparison of the results in the rabbits and human beings showed little difference. The accuracy of the skin titration was found to be within similar limits for rabbits and human beings, provided half as many more animals were used in the test. Two antitoxins could be differentiated by skin titration, if the potency of one was twice that of the other. Small differences in potency were not demonstrable by the method described.

EDNA DELVES.

SWARTZMAN'S PHENOMENON OF LOCAL SKIN REACTIVITY TO BACTERIAL PRODUCTS. F. M. BURNET, J. Path. & Bact. **34**:45, 1931.

The Shwartzman reagent is common to widely different bacterial groups. If material from *B. typhosus, meningococcus* or *B. pertussis* is used to prepare the skin, preparations from any of these organisms will give typical reactions when injected intravenously. Active preparations are readily obtained by Besredka's method of preparing "endotoxins," and the evidence points to the Shwartzman reagent being identical with these bodies. Local and general desensitization of prepared areas can be obtained by suitable injections. Material treated with formaldehyde can function as a provocative agent when it is injected intravenously, but when it is used to prepare the skin it gives an atypical reaction characterized by a central desensitization of varying extent, often sufficient to annul the reaction completely. The points of resemblance and of dissimilarity to anaphylactic reactions shown by the Shwartzman phenomenon are discussed.

AUTHOR'S SUMMARY.

THE INTERMEDIATE ZONE PHENOMENON IN CERTAIN BR. ABORTUS AGGLUTINATING SERA. F. W. PRIESTLEY, J. Path. & Bact. **34**: 81, 1931.

A curious zone of inhibition seen in certain serums from cattle affected with contagious abortion has been investigated. The following points have been demonstrated. The position of the zone depends on the ratio between the amount of serum and the organisms. Filtration through bacteriologic filters causes the zone to widen in the direction of stronger concentrations of serum. Heat (56 C.) in the absence of the organisms widens the zone, but in the presence of organisms causes the zone to narrow. The marked effect of saline in varying concentrations on the zone has been demonstrated. Experiments suggest that the zone is due to an insufficient reduction of potential on the bacteria in the dilutions within the zone.

AUTHOR'S SUMMARY.

AUTOPSIES ON FIFTY CHILDREN VACCINATED WITH B C G. J. ZEYLAND and E. PIASECKA-ZEYLAND, Ann. de l'Inst. Pasteur **43**:767, 1929.

Children who had died from causes other than tuberculosis were carefully examined. They had received oral administrations of B C G vaccine. Lesions were not produced even in premature or weakened infants. The organisms may traverse the digestive tract, but prolonged sojourn in the body does not increase their virulence, although sensitivity to tuberculin develops. For four weeks following vaccination, or until immunity is established, it is necessary to prevent the tuberculous infection of the vaccinated infant.

M. S. MARSHALL.

VACCINATION OF MAN AGAINST UNDULANT FEVER. C. DUBOIS and N. SOLLIER, Ann. de l'Inst. Pasteur **45**:596, 1930.

Preventive vaccination has been accomplished on 111 persons who had been exposed to *Brucella* infection (caprine, ovine, or bovine). No subjects vaccinated from three to eight months previously have actually contracted undulant fever. Two of thirty-six nonvaccinated controls were attacked. It is thus concluded that in regions in which animal brucelliasis exists, preventive vaccination is the only practical means of protecting man. In "contaminated" regions vaccination should be practiced on those coming in contact with infected animals. The vaccine that we used is entirely innocuous. (The vaccine consists of heat-killed suspensions of human, ovine, caprine, porcine and bovine cultures at a total of two billion organisms per cubic centimeter.) The duration of immunity can be determined only by longer experience with more vaccinations; the practical value of the method rests on this determination.

AUTHORS' SUMMARY.

THE LYSOZYME CONTENT IN THE CONJUNCTIVAL SAC AND IN THE TEARS. C. HALLAUER, Arch. f. Augenh. **103**:199, 1930.

The lysozyme content of the tears was determined in 120 patients who had (*a*) clinically normal conjunctivae, and (*b*) chronic and acute inflammations of the conjunctiva or cornea. The lysozyme content was always decreased in acute irritations of the anterior eye accompanied by abundant secretion of tears, or as the result of general disease (scrofulosis, lymphatic diathesis). It would appear, therefore, that the amount of lysozyme found in the tears is immediately dependent on the secretory activity of the lacrimal glands; it is decreased primarily by general diseases and secondarily by a hypersecretion induced by reflex. Atropine prevents the hypersecretion of tears and therefore tends to increase the amount of lysozyme, whereas in stimulating secretion, pilocarpine lowers the lysozyme content.

The significance of lysozyme as an antibacterial substance is demonstrated and its therapeutic use recommended. AUTHOR'S SUMMARY.

DIPHTHERIA PROPHYLAXIS BY MEANS OF LOEWENSTEIN'S DIPHTHERIA CULTURES IN VACCINE OINTMENT. E. URBANITZKY, Deutsche med. Wchnschr. **56**:1342, 1930.

To prevent diphtheria in a children's hospital the infants and children were inoculated three times at intervals of two months by rubbing increasingly large doses of unfiltered diphtheria cultures treated with formaldehyde into the skin. Of twenty-four children up to the age of 2 years, fifteen gave positive reactions to the Schick test. Six months after the treatment was started all gave negative reactions to the Schick test. This method of immunization was slightly less successful in older children, and of twenty-three adults who had been treated, only 63 per cent gave negative reactions to the Schick test. The incidence of diphtheria among the children in the hospital was reduced to nil. PAUL BRESLICH.

CEREBRAL IMMUNIZATION AGAINST DIPHTHERIA TOXIN. U. FRIEDEMANN and A. ELKELES, Klin. Wchnschr. **9**: 1907, 1930.

In rabbits the immune response obtained through the intracerebral injections of diphtheria toxin is much greater than that obtained through intravenous injection.

EDWIN F. HIRSCH.

IMMUNITY REACTIONS IN SYPHILIS. H. KROÓ and N. v. JANCSÓ, Klin. Wchnschr. **10**:105, 1931.

A serum resistant variant of *Spirochaeta pallida* may be produced by gradual adjustment to immune serum. These resistant spirochetes lose their ability to stimulate spirocheticidal antibodies, but retain the property of provoking complement-binding substances. Inoculation of the serum resistant spirochetes into ordinary mediums leads to a recovery of the antigenic properties.

AUTHORS' SUMMARY.

THE MECHANISM OF DESENSITIZATION OF THE ALLERGIC SKIN. W. STORM VAN LEEUWEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**:1, 1930.

In the case of sensitization to various substances, desensitization by means of a particular antigen usually results in a local desensitization to other antigens as well. The question whether this desensitization is dependent on an "intermediary substance is discussed.

BACTERIAL LIPOIDS. M. GUNDEL and W. WAGNER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**:63, 1930.

Various bacterial lipoids are bactericidal due to their content of fatty acids. The antigenic and bactericidal properties of bacterial lipoids are not identical.

THE ANTIGENIC GROUPING OF THE COLON BACILLI. M. GUNDEL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**:99, 1930.

The colon bacilli fall into various antigenic groups, all of which have certain common antigenic properties.

CHEMICAL NATURE OF HETEROGENETIC ANTIGEN IN SHIGA BACILLI. K. MEYER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**:134, 1930.

The heterogenetic antigen in Shiga bacilli is not attached by pepsin or trypsin and resists treatment with sodium hydroxide at 100 C. for one hour, but hydrochloric acid destroys it promptly. Consequently, it seems highly improbable that the antigen is of protein nature, and the claim that it is a carbohydrate seems to be strengthened.

AN UNUSUALLY HIGHLY DEVELOPED ANAPHYLACTIC STATE IN THE GUINEA-PIG. R. DOERR and S. SEIDENBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**:169, 1930.

After passive sensitization to horse serum by means of specific rabbit serum, guinea-pigs may die from shock after the intravenous injection of 0.002 cc. of horse serum. Congenitally sensitized pigs may suffer fatal shock from 0.0008 cc. of horse serum injected intravenously, and such pigs may die from shock even when the horse serum (from 0.2 to 2 cc.) is introduced subcutaneously; in the latter case, however, the symptoms develop only after a latent period of from fifteen to twenty-five minutes.

Microbiology and Parasitology

DIPHTHERIA OF THE UMBILICUS. J. C. MONTGOMERY, Am. J. Dis. Child. **40**: 968, 1930.

The case of an infant with umbilical diphtheria complicated by postdiphtheritic paralysis and myocarditis is reported, with complete bacteriologic and pathologic observations and a brief review of the literature. It has been impossible to discover in the literature another case of diphtheria limited solely to the umbilicus in which there were myocardial or neurologic complications.

AUTHOR'S SUMMARY.

SONNE DYSENTERY. RICHARD L. NELSON, Am. J. Dis. Child. **41**:15, 1931.

Attention is drawn to the possible importance of *B. dysenteriae* Sonne as a cause of dysentery in children. Methods for the isolation and identification of the Sonne bacillus are given. Clinical features of the disease with case histories and clinical charts illustrative of the mild and severe forms are given.

AUTHOR'S SUMMARY.

ULCERATIVE LARYNGITIS DUE TO CORYNEBACTERIUM ULCERANS. JESSE G. M. BULLOWA and MENDEL JACOBI, Am. J. Dis. Child. **41**:120, 1931.

A case of fatal ulcerative laryngitis due to an atypical diphtheria-like organism and producing only a slight fibrinous reaction is reported. The organism cultured from a laryngeal ulcer is identified as the *Corynebacterium ulcerans* of Gilbert and Stewart, previously isolated only from nonfatal upper respiratory infections. Both organisms produce extensive necrosis and ulceration without the formation of typical diphtheritic pseudomembrane. The immunologic study of cases of diphtheria not responding to antitoxin is suggested.

AUTHORS' SUMMARY.

DEATH IN INFECTIONS WITH TRYPANOSOMA EQUIPERDUM IN RATS. JUSTIN ANDREWS, CARL M. JOHNSON and V. J. DORAML, Am. J. Hyg. **12**:381, 1930.

It is believed that *T. equiperdum* causes death, by asphyxiation, of the rat host into which it is experimentally introduced. This is brought about by pulmonary edema due to partial obstruction of the circulation by the agglutination of the trypanosomes in the heart and lungs. The consequent anoxemia leads to a nonvolatile, uncompensated acidosis and to central necrosis of the liver, interfering with both its glycogenic and its glycogenolytic functions and ultimately producing hypoglycemia.

AUTHORS' SUMMARY.

EXPERIMENTAL AMEBIASIS IN KITTENS. Kentaro Hiyeda, Am. J. Hyg. **12**:401, 1930.

It is attempted to explain the manner of invasion into the tissues of the colon by *Entameba histolytica,* experimentally injected rectally into a limited number of kittens. In the cases showing *E. histolytica* in the stools during the first twelve hours after injection, the mucosa of the colon displays minute follicular ulcerations, and the superficial capillaries are engorged with leukocytes. Up to forty-eight hours following injection, the colitis produced is typical of any acute colitis, and no ameba can be demonstrated in the tissue. Thereafter, different sized, ulcerated areas appear in the mucous membrane of the colon, and microscopically their walls appear coated with tissue débris, mucus, plasma and amebae. A new conception of the mode of invasion is presented. From the superficial ulcers in the mucous membrane, the ameba spread laterally along the collagenous fibers of the submucosa and also through the membrana propria. The deep submucosa is invaded, and Lieberkuhns' glands are in turn invaded from their basal side. Following this the epithelium exfoliates at the basal membrane, and the amebae occupy the empty spaces. The submucosa is invaded by way of the fibrous tissue, and not through the lumina of Lieberkuhns' glands.

P. H. GUINAND.

RHINOSPORIDIUM SEEBERI: PATHOLOGICAL HISTOLOGY AND REPORT OF THE THIRD CASE FROM THE UNITED STATES. C. V. WELLER and A. D. RIKER, Am. J. Path. **6**:721, 1930.

The first description of *Rhinosporidium seeberi* was published in a thesis from Buenos Aires in 1900 by Guillerino Seeber, and since that time there have appeared in the literature at least twenty-five case reports from India and Ceylon, several of them dealing with the occurrence of infection in anatomic locations other than the nose. Three cases of this parasitic infection have been reported from Argentina and three widely scattered cases from the United States. In no instance is there any certainty concerning the mode of infection and transmission. The possibility of an animal host, probably among the larger farm animals, seems logical in view of a history, in most cases, of exposure to such animals. All efforts at experimental animal inoculation, however, have given negative results. It seems remarkable that not one of the thirty or more cases reported has been in the female. The gross lesion in the nose is described as a reddish-purple, raspberry-like polypus, which externally presents no features attracting particular attention. A close examination of the cut surface, however, reveals the larger parasites as white spots of pinpoint size. Histologically, a moderately edematous, vascular, connective tissue stroma is observed peppered with characteristic parasitic cysts, each a single organism in various stages of development. The cysts average 100 microns in diameter, being surrounded by a doubly contoured chitinous-appearing capsule. The mature cysts contain many spores, which on rupturing are followed by a local proliferative foreign-body reaction in the polypus.

C. G. WARNER.

NEUROVACCINIAL AND HERPETIC MENINGO-ENCEPHALITIS IN RABBITS. E. T. C. SPOONER, Am. J. Path. **6**:767, 1930.

The histologic observations in six neurovaccinal and four herpetic brains are described. Intranuclear inclusion bodies are found to be the only sure distinctive feature of the herpetic disease. In other respects the two diseases are essentially similar. In neurovaccinia, the meningitis is the most conspicuous observation, both clinically and histologically. Various spontaneous lesions in the brains of uninoculated laboratory rabbits are discussed. Changes in the myelin sheaths are described in the brains of herpetic and vaccinal animals, but perivascular demyelinization of the kind characteristic of postvaccinal encephalitis in man was not seen. It is possible that the duration of the disease is a factor in the development of such a condition. Since preparing this paper for publication, valuable articles on the histology of neurovaccinal encephalitis in monkeys and rabbits, by Hurst and Fairbrother and by McIntosh and Scarff, have appeared in the *Journal of Pathology and Bacteriology* (**33**:463 and 483, 1930). These papers are in agreement on the cardinal points of histology, such as the absence of inclusion bodies and the accentuation of the meningitis. In neurovaccinia, McIntosh and Scarff emphasize the rôle of the vascular endothelium; this is undoubtedly damaged in the smaller vessels, and there are occasional evidences of its proliferation, but from the preparations in this investigation the impression is derived that this feature of the disease is subsidiary to the general inflammation, and, moreover, it seems to be just as much a feature of herpetic encephalitis as it is of neurovaccinal encephalitis.

AUTHOR'S SUMMARY.

THE IDENTITY OF YELLOW FEVER LESIONS IN AFRICA AND AMERICA. OSKAR KLOTZ and T. H. BELT, Am. J. Trop. Med. **10**:299, 1930.

In our studies we have found that the quality of the lesions arising in yellow fever in Africa is similar to that of lesions occuring in American cases. Furthermore, the incidence of various types of changes in different tissues is broadly the same, with differences only in a few reactions which may be accounted for by the technic applied. In these more careful studies, applied to a larger number of cases, we have confirmed our previous observations that the nature of the pathologic processes arising in the yellow fever of Africa is identical with that of such processes occurring in American cases. Variations that have been observed in the quality of the lesions here described are compatible with the variations that have been found in different strains of virus isolated in America and in Africa.

AUTHORS' SUMMARY.

CALABAR SWELLING IN LOA PATIENT. ASA C. CHANDLER, GIBBS MILLIKEN and VICTOR T. SCHUHARDT, Am. J. Trop. Med. **10**:345, 1930.

The appearance of three Calabar swellings on distant parts of the body of a patient infected with *Loa* worms following the release of some of the body fluids of a *Loa* worm under the conjunctiva at the time of its extraction, together with the production of a typical Calabar swelling by the injection of a filarial antigen, affords strong, if not conclusive, evidence for the allergic nature of these swellings, as first suggested by Fulleborn.

AUTHORS' SUMMARY.

THE TROPICAL RAT MITE AS THE CAUSE OF A SKIN ERUPTION AND VECTOR OF ENDEMIC TYPHUS FEVER. BEDFORD SHELMIRE and WALTER E. DOVE, J. A. M. A. **96**:579, 1931.

Approximately 200 cases of "rat mite dermatitis" are reported from Dallas, Texas, and neighboring towns. From persons having evidence of mite bites, and from their residences or places of work, mites were collectetd and identified as *Liponyssus bacoti* Hirst. At Dallas, Fort Worth, Henderson and Longview, Texas,

mites were collected from rats and were identified as *Liponyssus bacoti*. In the same places, 11 proved cases and approximately 125 cases of suspected endemic typhus were reported. The advent and coincidental occurrence of endemic typhus and the tropical rat mite in northern and eastern Texas suggest that these parasites may be vectors of the disease.

AUTHORS' SUMMARY.

THE TRANSMISSION OF PERIODIC OPHTHALMIA OF HORSES BY A FILTRABLE AGENT. ALAN C. WOODS and ALAN M. CHESNEY, J. Exper. Med. **52**:637, 1930.

A filtrable agent has been obtained from the humors and tissues of the eyes of horses suffering from active periodic ophthalmia. The intravitreous injection of this filtrate produced in normal horses the same clinical and pathologic picture observed in the natural disease. When injected into rabbits, the filtrate produced a different clinical picture, but the essential pathologic lesions closely resembled those found in horses. After passage of the filtrable agent through six generations of rabbits, it again produced the clinical and pathologic picture of the natural disease when injected into the eyes of normal horses. It appears, in this epidemic at least, that this filtrable agent was the specific etiologic factor of the periodic ophthalmia.

AUTHORS' SUMMARY.

TYPHUS FEVER. H. ZINSSER and M. RUIZ CASTANEDA, J. Exper. Med. **52**:865, 1930.

In guinea-pigs inoculated with washed *Rickettsiae* from Mexican typhus fever a disease develops identical with that resulting from inoculations with whole tunica scrapings, blood or other virulent material, and the animals thereby become immune to European typhus fever. The etiologic agent of Mexican typhus fever is the *Rickettsia* body of the type described by Mooser in the tunica vaginalis of infected guinea-pigs. It is likely that the etiologic agent of European typhus fever is an organism similar to this, but not identical with it in some of its minor biologic characteristics.

AUTHORS' SUMMARY.

THE INTRA-AURAL ADMINISTRATION OF CERTAIN BACTERIA ASSOCIATED WITH MIDDLE EAR DISEASE IN ALBINO RATS. J. B. NELSON, J. Exper. Med. **52**:873, 1930.

The infective capacity of three bacteria commonly encountered during a study of natural disease of the middle ear in a rat colony has been determined by direct intra-aural injection into young rats. One week after the introduction of *B. actinoides*, 75 per cent of the rats showed a purulent exudate in the middle ear cavity into which the injection was made, and 65 per cent yielded pure cultures of the organism. With hemolytic and nonhemolytic streptococci, 75 per cent showed a serous or mucoid exudate, and 12 per cent yielded the organism in culture. With a diphtheroid, 18 per cent showed a gross reaction in the middle ear which was sterile in every case. The experimental observations are discussed in relation to the etiology of disease of the middle ear.

AUTHOR'S SUMMARY.

STREPTOCOCCI IN INFECTIOUS ARTHRITIS AND RHEUMATIC FEVER. R. N. NYE and E. A. WAXELBAUM, J. Exper. Med. **52**:885, 1930.

On using the technic described by Cecil and his associates in chronic infectious arthritis, only one positive culture, a diphtheroid, was obtained in ten cases of chronic infectious arthritis and sterile cultures in eleven cases of infectious arthritis and twelve cases of rheumatic fever. A second series was studied, the technic described by Cecil in rheumatic fever being used. Synovial fluid, lymph glands and subcutaneous nodules, as well as the blood, were cultivated. Seven different organisms were isolated. Since the same organism was not found in duplicate cultures, the authors believe their positive results to be due to contaminations.

L. E. COOLEY.

STUDIES ON TUBERCULOSIS: I. REACTION OF THE CONNECTIVE TISSUES OF THE NORMAL RABBIT TO LIPOIDS FROM THE TUBERCLE BACILLUS, STRAIN H-37; II. REACTION OF THE CONNECTIVE TISSUES OF THE NORMAL RABBIT TO A WATER-SOLUBLE PROTEIN AND A POLYSACCHARIDE FROM THE TUBERCLE BACILLUS, STRAIN H-37: SPONTANEOUS PSEUDO-TUBERCULOSIS ASPERGILLINA AS A COMPLICATION IN FRACTION TESTING; III. THE DERIVATION OF GIANT CELLS WITH ESPECIAL REFERENCE TO THOSE OF TUBERCULOSIS; IV. THE RELATION OF THE TUBERCLE AND THE MONOCYTE-LYMPHOCYTE RATIO TO RESISTANCE AND SUSCEPTIBILITY IN TUBERCULOSIS. F. R. SABIN, C. A. DOAN and C. E. FORKNER, J. Exper. Med. (supp. no. 3), 1930, p. 1.

I. The lipoid fraction from the tubercle bacillus contains maturation factors for monocytes, epithelioid cells and epithelioid giant cells. The most important component of the lipoids for biologic investigation is the phosphatide A-3, since it produces the most massive reaction toward epithelioid cells and epithelioid giant cells, and also because it is the only partition of the lipoids that acts as an antigen. The stimulus to the formation of tubercles resides in certain fatty acids of high molecular weight found in tubercle bacilli. These fatty acids are present in the four major partitions of the lipoids and account in each instance for their specific activity. The most potent fatty acid in the production of tubercles is that derived from the phosphatide. The purified, optically active phthioic acid obtained from the glyceride fraction, in small dosage, produces epithelioid cells, but more nonspecific connective tissue; the optically inactive tuberculostearic acid is relatively inert. The specific tuberculous tissue resulting from the intraperitoneal injection of the phosphatide from the tubercle bacillus undergoes resorption. Two mechanisms in its disappearance similar to those operating in the disease have been seen: caseation in which masses of degenerating epithelioid cells become infiltrated with leukocytes, and phagocytosis of the cellular débris by clasmatocytes, without caseation. Besides the specific reaction of the lipoids, these factors also produce a marked growth of nonspecific connective tissue cells, without, however, any reaction toward fibrous tissue in the acute stages. All the subfractions from the lipoids are irritating when injected into the peritoneal cavity, calling leukocytes into the tissues and stimulating clasmatocytic activity. The unsaponifiable substance from the purified wax is particularly active in producing an extreme general reaction of connective tissue cells.

II. From these studies we conclude that the water-soluble protein from the tubercle bacillus, when not denatured, is toxic to normal rabbits, inducing fever and hemorrhage when introduced intravenously, but it is not lethal except in massive doses. By the intraperitoneal route it is less toxic, but calls forth a local response of leukocytes and phagocytes without any striking proliferation of new connective tissue. Damage to the endothelium is indicated by hemorrhage, chiefly in the bone marrow. Tuberculous guinea-pigs succumb rapidly to protein 304 when given intraperitoneally. The polysaccharide is nontoxic when introduced intravenously into the normal animal; when introduced intraperitoneally, on the other hand, it is irritative, and each succeeding dose continues to elicit a fresh emigration of leukocytes from the vessels. These leukocytes appear to be damaged, for they are actively engulfed by clasmatocytes. Guinea-pigs with extensive tuberculosis may die soon after subcutaneous or intraperitoneal injections of the polysaccharide. Aspergillina fungus may produce a pseudotuberculous lesion, resembling, both macroscopically and microscopically, the cellular reaction of tuberculosis. The absence of positive skin tests with old tuberculin when such lesions are present, as furthermore when tuberculous tissue has been produced by chemical stimulation with the tuberculophosphatide, emphasizes the necessity for considering tubercle formation as a mechanism apart from allergy in tuberculosis.

III. There are two types of giant cells discriminated by their method of formation; one is derived from a single monocyte or epithelioid cell and the other by the fusion of cells. The epithelioid giant cell is formed by amitotic nuclear division; it tends to be small, simple and relatively uniform in structure; its

essential structure is a rosette of fine vacuoles which in the living state are stainable with neutral red. The foreign body types show extreme variation in size and structure, according to the nature and the number of the cells out of which they are made. They lack any constant cytoplasmic pattern. Both of these types of giant cells are probably formed in response to the need for phagocytosis of foreign material. In tuberculosis it is probably only certain specific portions of the lipoids that induce the production of mononucleated and multinucleated epithelioid cells. The stimuli for the formation of giant cells of the foreign body type are much more varied than those that produce epithelioid giant cells.

IV. In rabbits receiving a standard dose of bovine tubercle bacilli, a high preinfection monocyte-lymphocyte ratio in the circulating blood has been correlated with the development of an acute fulminating tuberculous infection; but with an average or low index, the course of the disease has varied. Susceptibility has been further marked by the promptness with which the monocyte-lymphocyte index rose after infection and with its maintenance at a high level; resistance, on the other hand, has been evidenced by a continued low index. The monocyte-lymphocyte index is one measure of resistance to tuberculosis. Some evidence has been presented to show that when monocytes, the forerunners of the epithelioid cell, are decreased through the action of an antiserum, a greater proportion of the animals survive into the chronic stage of the disease than do the controls. The production of tuberculous tissue in considerable quantity by injection into the tissues of the phosphatide or liquid saturated fatty acid from the tubercle bacillus does not render the animal allergic, and seems definitely to lower resistance to the disease on subsequent infection with tuberculosis. The degree to which the tissues react specificially with the formation of new epithelioid cells is indicated by the amount of the change in the monocyte-lymphocyte index in the blood. The differences observed in individual animals in the amount of tissue reaction to a given amount of phosphatide derived from the tubercle bacillus are definite and are similar to those long noted in connection with humoral antigen-antibody responses with proteins. Both in tuberculosis and after intraperitoneal injections of the phosphatide, the relationship of monocyte to lymphocyte in the blood before death has been a measure of the extent of the epithelioid and lymphoid proliferation found at autopsy. Hence, the monocyte-lymphocyte ratio can be taken as an index of the relative abundance of these cells in the tissues. Antigenic intravenous doses of the phosphatide, or of antiphosphatide serum, given either before or after infection, may give a slight protection to an animal if the dose of infecting organisms is not too great. Taken together, the observations of the present paper implicate the monocyte and its derivative, the epithelioid cell, when harboring living bacilli, as factors in the spread of tuberculosis in the animal. The type of reaction of an animal to the lipoids of the tubercle bacillus, whether predominately cellular or humoral, may be a decisive factor in determining resistance on the one hand and susceptibility on the other.

AUTHORS' SUMMARIES.

BORIC ACID FOR THE PRESERVATION OF MILK NATURALLY INFECTED WITH BRUCELLA ABORTUS. J. TRAUM and B. S. HENRY, J. Infect. Dis. **47**:380, 1930.

Boric acid in 1 per cent concentration is a convenient, efficient and safe preservative for milk that is to be injected into guinea-pigs to determine the presence or absence of *Brucella abortus*.

AUTHORS' SUMMARY.

THE GROWTH AND TOXIN PRODUCTION OF CORYNEBACTERIUM DIPHTHERIAE IN SYNTHETIC MEDIUMS. M. E. MAVER, J. Infect. Dis. **47**:384, 1930.

The synthetic medium devised by Braun and Hofmeier was found to afford a better basic medium for the study of growth and toxin production of *C. diphtheriae* than the medium of Uschinsky, Hadley or Dolloff. The comparative nutritive values of ten amino-acids were studied, three strains of Park 8 and three more

recently isolated strains being employed. The simple mono-amino-acids, such as alanine, phenylalanine, valin and especially glycine, were more effective in stimulating growth in a synthetic medium than the more complex mono-amino-acids that were tried. The nitrogen-bearing constituents of the Braun and Hofmeier medium were modified considerably before moderate production of toxin was obtained. The cystine content was increased fourfold, to the point of maximum solubility in this solution, asparagin or ammonium succinate replaced the sodium aspartate, and glycine was added. A virulent strain, 4703, one strain of Park 8 and an avirulent strain, 4104, were adapted to growth on synthetic mediums. The virulent strain 4703S produced toxin on synthetic mediums after six months' cultivation on protein-free mediums. The most potent toxin produced by strain 4703S had a minimal lethal dose of 0.1 cc. and a skin test dose of 0.0001 cc. Strain Park 8T elaborated a weaker toxin in synthetic mediums, with a minal lethal dose of 0.5 cc. and a skin test dose of 0.0005 cc. The experiments described seem to indicate that several factors control the production of toxin in synthetic mediums. Its appears that the strain must be thoroughly adapted to rapid growth and formation of pellicle in protein-free medium. It appears, further, that the medium must provide not only nutrients for growth and pellicle formation, but these nutrients should also favor the appearance or maintenance of the toxigenic variants that occur in consequence of a dissociative process.

AUTHOR'S SUMMARY.

EXPERIMENTAL RABIES IN WHITE MICE AND ATTEMPTED CHEMOTHERAPY. A. HOYT and C. W. JUNGEBLUT, J. Infect. Dis. **47**:418, 1930.

Typical and constant rabies may be produced in white mice by intracerebral injection of fixed virus. A dose of virus approximating a minimum lethal dose may be determined. Prophylactic administration of various drugs (particularly arsenicals and quinine derivatives) failed to protect animals infected intracerebrally by single or multiple minimal lethal doses. The period of incubation of the disease consistently showed a very slight prolongation following injection of silver arsphenamine.

AUTHORS' SUMMARY.

THE IDENTIFICATION OF A STREPTOTHRIX ISOLATED FROM A HUMAN BEING INFECTED WITH IT. G. MEHRTEN and R. S. MUCKENFUSS, J. Infect. Dis. **47**:425, 1930.

Reports of infections with *Streptothrix* have been accumulating for many years. Although clinical data are fairly abundant, bacteriologic data are incomplete in most of the reports of cases. The accompanying table gives the characteristics in some cases reported in the literature, as well as the characteristics of the strain isolated at Barnes Hospital. Bacteriologic studies in many reports were not extensive enough to make their inclusion in this table practical. Those cases in which the organisms formed granules in tissue or pronounced swellings at the ends of the filaments in culture were not included. Only a few studies on the fermentation of sugars by this organism are reported in the literature. The organism isolated by Giddings did not ferment dextrose, lactose, saccharose or mannite. Neither did it produce hemolysis. The strain isolated by Blake from a case of rat-bite fever did not ferment dextrose, inulin, lactose, mannite, raffinose, saccharose or salicin. Serologic studies were made by Claypole, who used the complement-fixation reaction. The serums showed cross-reactions with other members of the group, as well as with tubercle and lepra bacilli, so that the method was not satisfactory for classification. It is evident from a review of the literature that the strains of *Streptothrix* that have been described differ markedly in their characteristics as observed by ordinary bacteriologic methods. Any further subdivision of the group by the present methods of study is impracticable and of no significance as regards the type of disease. The strain that we have isolated approaches most nearly in its characteristics that described by Horst.

AUTHORS' SUMMARY.

TYPES OF BRUCELLA IN ONE HUNDRED AND TWENTY-NINE CASES OF UNDULANT FEVER. W. N. PLASTRIDGE and J. G. MCALPINE, J. Infect. Dis. **47**:478, 1930.

One hundred and twenty-nine strains of the genus *Brucella* isolated from cases of undulant fever in the United States and Europe were classified by Huddleson's dye plate method and by their ability to utilize dextrose. Sixty-three of these strains were found to be of the bovine type of *Br. abortus* and the remaining sixty-six of the porcine type. The average, minimum and maximum amounts of available (1 per cent) dextrose utilized by the two types of *Br. abortus* of human origin are as follows: bovine type, 0.88 per cent, none and 3, respectively; porcine type, 10 per cent, 3.3 per cent and 18.2 per cent, respectively. The results obtained by Huddleson's dye plate method were in close agreement with those obtained by the dextrose utilization method.

AUTHORS' SUMMARY.

DECOMPOSITION OF UREA BY BACILLUS PROTEUS. A. A. DAY, W. M. GIBBS, A. W. WALKER and R. E. JUNG, J. Infect. Dis. **47**:490, 1930.

Bacillus proteus was cultivated in plain, dextrose urea and urea-dextrose urea broths. Dextrose exerted a sparing action for the protein, but in the urea broth increased the formation of ammonia. When, however, the markedly greater number of organisms in the dextrose urea broth, attributable to the maintenance of a more favorable reaction for growth by the interaction of the end-products of dextrose and the breakdown of urea, is considered, it becomes apparent that less hydrolysis of urea per unit volume of organisms occurred than in the plain urea broth. The same mechanism was responsible for the greater destruction of dextrose observed in the presence of urea. In actively growing cultures of *B. proteus* in urea broth, a very small amount of growth brought about a marked breakdown of urea, whereas massive growths of organisms that were not reproducing (resting) were required to produce an equivalent change. With the latter, the urea-splitting was roughly proportional to the mass of the organisms. Urea did not meet the nitrogen requirements of the organism, as tested in a variety of synthetic mediums. The inference is warranted that the urea activity is only incidental to the metabolism of the organism and not concerned with its vital needs. Great difference in morphology was encountered when *B. proteus* was cultured on plain agar, dextrose agar and urea agar. Further confirmation of the endocellular nature of the enzyme was found in the ability of chloroform-killed, washed organisms to hydrolyze urea. Organisms so killed were decidedly less effective than vigorously reproducing bacteria. The addition of dextrose to the urea solution augmented the urease activity of moist chloroform-killed organisms, but was without influence on dried chloroform-killed organisms.

AUTHORS' SUMMARY.

HUMAN CARRIERS OF STREPTOCOCCUS EPIDEMICUS. I. PILOT, B. HALLMAN and D. J. DAVIS, J. Infect. Dis. **47**:503, 1930.

Streptococcus epidemicus is found in the throats of persons during interepidemic periods. The chief habitat appears to be the crypts of the faucial tonsils. Three carriers of *S. epidemicus* had enlarged tonsils, cervical adenitis and arthritic pains. The recognition of these carriers is important because of their possible rôle in the transmission of the disease to others and particularly in the accidental infection of the udder of the cow, with subsequent explosive epidemic sore throat spread through the milk.

AUTHORS' SUMMARY.

SPORADIC SEPTIC SORE THROAT DUE TO STREPTOCOCCUS EPIDEMICUS. I. PILOT and D. J. DAVIS, J. Infect. Dis. **47**:507, 1930.

The three cases were all sporadic. The source of infection was undetermined. It is possible that in such sporadic cases, carriers of *S. epidemicus* are the source

of infection, but milk as a source cannot as yet be ruled out. Investigations bearing on possible sources are being made. Recently, we recognized *S. epidemicus* in the exudates of active otitis media, mastoiditis and cervical adenitis. The throats did not reveal acute tonsillitis. However, *S. epidemicus* may be present in the throat cultures. Some of the patients had a definite history of tonsillitis, but others were apparently well until otitis media developed. It would appear that *S. epidemicus* may also cause mild inflammations of the throat or upper respiratory passages, which may be complicated by acute otitis media and mastoiditis.

AUTHORS' SUMMARY.

HERPES ENCEPHALITIS IN MONKEYS OF THE GENUS CEBUS, WITH OBSERVATIONS ON THE GREEN STREPTOCOCCUS. E. B. MCKINLEY and M. DOUGLASS, J. Infect. Dis. **47**:511, 1930.

Herpetic encephalitis has been produced in five of nine monkeys of the genus *Cebus*. The disease in its acute and subacute form closely resembles human encephalitis. The pathologic lesions are also similar to those of the human malady, except for the presence of intranuclear herpetic inclusion bodies in the ganglion cells of the cortex. The disease kills *Cebus* monkeys in from six to eleven days. Secondary invading streptococci were demonstrated in the brain of one monkey. Healthy monkeys receiving an emulsion of the brain of this monkey did not show any streptococci, either on cultivation of the brain or on inoculation of it into rabbits. Our studies indicate that the green streptococcus is not related to the virus infection in question, but that this microbe may, in occasional animals under optimum conditions, invade the central nervous system after the "soil" has been previously prepared by the virus. We therefore see no reason for attaching an etiologic relationship to the green streptococcus in such a disease as encephalitis. Difficulty has been met with in attempting to transmit herpes encephalitis from monkey to monkey. This may be due to the chance selection of refractory animals, or in some manner a neutralization of the herpes virus may occur in the brains of some monkeys.

AUTHORS' SUMMARY.

EXPERIMENTAL STUDY OF DENGUE FEVER. G. BLANC and J. CAMINOPETROS, Ann. de l'Inst. Pasteur **44**:367, 1930.

In an extensive report of sixty-nine pages, the subjects of transmission by insects, infection of laboratory animals, immunity, properties of the virus and vaccination are discussed. It is noted that *Stegomyia*, which were maintained as long as 228 days in the laboratory, may acquire the virus from the blood of a patient up to the fifth day of the disease; they become infective after eight days and remain so for at least 174 days, or virtually for life, if kept in a temperature of 20 C. or higher. Animal experiments were successful in four genera of monkeys; dogs and rabbits were negative, and rats were doubtful, but a silent or inapparent infection occurs in guinea-pigs, monkeys and man. A firm immunity seems to be assured following an attack, but convalescent serum fails. There was no apparent cross-immunity with yellow fever serum. The virus is not preserved by drying. Bile-treated, inactive virus conferred no immunity, although repeated inoculations indicate some degree of immunity. Double vaccination was performed with (1) bile-treated (1:15) inactive virus and with (2) bile-treated (1:20) virus immunized against a heavy dose of active virus.

M. S. MARSHALL.

THE GROWTH OF ANAEROBES IN RELATION TO POTENTIAL OF MEDIUM. HARRY PLOTZ and JEAN GELOSO, Ann. de l'Inst. Pasteur **45**:613, 1930.

Potentiometric and colorimetric studies on the changes in the ox-red potential in cultures of anaerobes are reported. Sterile broth develops an rH_2 of 7.5 at 37 C., which corresponds to that developed by dextrose alone. A limiting value of rH_2 of 5.5 is developed during the growth of anaerobes. This change in

potential is analogous to that produced by the addition of platinum black to the broth and indicates that the dehydrogenation of the dextrose is catalyzed by the growth of the micro-organisms. The results show that a rapid growth of anaerobes is obtained only when the rH_2 lies between 0 and 14. C. E. CLIFTON.

RELATION OF BACTERIUM GRANULOSIS TO TRACHOMA. P. K. OLITSKY, Rev. internat. du trachome **7**:173, 1930.

Up to the present, typical bodies, either intranuclear or cytoplasmic, such as characterize true filtrable virus diseases, have not been found in trachoma. Although this work is still in progress, the tentative opinion at this moment is that whenever bodies are seen, they can be shown to be bacteria, artefacts, pigment or structures similar to those found in preparations of smears taken from normal human or simian tissues.

In an experiment in which twelve macaques were employed, we have found that *Bacterium granulosis* is inactive in monkeys that are immune to the organism, but that it is specifically pathogenic in those that are normal and in those that are immune to spontaneous folliculosis. Conversely, the suspensions of tissue derived from a monkey with spontaneous folliculosis induce a follicular conjunctivitis in normal monkeys and in those immune to *Bacterium granulosis,* but are inactive in macaques that are resistant to the spontaneous disease.

CHARLES WEISS.

ENLARGEMENT OF THE SPLEEN IN UNDULANT FEVER. H. SCHOTTMÜLLER, Deutsche med. Wchnschr. **56**:1813, 1930.

An enormous enlargement of the spleen in a case of undulant fever is reported. The presence of a large spleen should direct attention to the possibility of undulant fever.

HEPATITIS AND CHOLECYSTITIS, A SPECIFIC COMPLICATION OF SCARLET FEVER TOXIN. H. SCHOTTMÜLLER, Klin. Wchnschr. **10**:17, 1931.

From a clinical study of four patients and a clinical anatomic study of a fifth patient, the author concludes that the streptococcus toxin of scarlet fever is responsible for certain changes in the liver and gallbladder.

Fahr reports the anatomic study of Schottmüller's fifth patient (*Klin. Wchnschr.* **10**:20, 1931), and describes the exudates of plasma cells, lymphocytes, histiocytes and eosinophilic leukocytes in Glisson's capsule of the liver, especially around the small bile ducts. Of special interest were the focal proliferative changes in the intima of the hepatic veins and the extensive cellular infiltrations of the entire wall. In addition, the wall of the gallbladder was diffusely infiltrated with cellular exudates. Fahr does not consider these changes specific. EDWIN F. HIRSCH.

THE GROWTH FORMS AND VIRULENCE OF HEMOLYTIC STREPTOCOCCI. H. SCHOTTMÜLLER, Klin. Wchnschr. **10**:107, 1931.

Hemolytic streptococci conserved for a time on silk threads or treated with chemicals, under the influence of animal and human tissues, are so modified that they form green colonies instead of hemolytic ones. The green colony form is avirulent. AUTHOR'S SUMMARY.

A PARATYPHOSUS B EPIDEMIC. A. PIERACH, München. med. Wchnschr. **77**: 2181, 1930.

An explosive epidemic during which about sixty persons became infected with paratyphoid B organisms occurred in a hotel. The infections were due to food supposedly contaminated by a carrier in the kitchen. The routine examination of persons who handle food for carriers of disease is again emphasized.

EDWIN F. HIRSCH.

INCLUSION BODIES IN HERPES SIMPLEX. HOTORI WATANABE, Zentralbl. f. Bakteriol. **116**:38, 1930.

Watanabe scarified the cornea and skin of rabbits, applied herpes virus Basle III of Doerr and herpes virus Dahlem of Gildemeister and Herzberg and examined sections taken from one to seven days thereafter. Inclusion bodies that resembled Guarnieri bodies were found in the cytoplasm of the epithelial cells as well as in the connective tissue cells of the substantia propria. Inclusion bodies of the type described by W. Löwenthal were not found. One colored plate is shown.

PAUL R. CANNON.

THE PATHOGENESIS OF TYPHOID INFECTIONS. ALICE WALDMANN, Zentralbl. f. Bakteriol. **116**:68, 1930.

The author infected mice with the Breslau strain of *Bacillus enteritidis*, by subcutaneous, intravenous and enteral methods, and studied the histopathologic effects, in an attempt to determine whether or not such infections are enteral or hematogenous in origin. With the subcutaneous and intravenous methods, the principal changes occurred in the liver and spleen as nodules of histiocytic components, whereas Pyer's patches and mesenteric lymph nodes were unaffected. The latter were affected only when the micro-organisms were fed, followed later by the characteristic nodules of focal necrosis in the liver and the spleen.

The conclusions drawn are that these experiments offer no support to the views of Sanarelli, Besredka and others that the typhoid infections are primarily hematogenous with later localization in susceptible tissues, i. e., the lymphoid structures of the intestinal tract. Rather, the evidence supports further the conception that the intestinal manifestations are the reactions of the lymphatic apparatus to the primary infection through the intestinal mucosa.

PAUL R. CANNON.

PROTECTION OF THE SPLEEN AND THE RETICULO-ENDOTHELIAL SYSTEM AGAINST SPIROCHAETA DUTTONI AND TRYPANOSOMA GAMBIENSE. T. H. AMAKO, Zentralbl. f. Bakteriol. **116**:280, 1930.

Amaka found that the combination of splenectomy and blockade markedly reduced the resistance of mice to *Spirochaeta duttoni* and of guinea-pigs to *Trypanosoma gambiense*, the death rate being as high as 95 per cent. Compensation of the remainder of the reticulo-endothelial system occurred within four days after splenectomy. Partial splenectomy and implantation of the spleen after previous splenectomy also ensured favorable protective effects.

PAUL R. CANNON.

EXPERIMENTAL SYPHILIS OF RABBITS. T. TANI, M. KAKISHITA and K. SAITO, Zentralbl. f. Bakteriol. **116**:471, 1930.

The authors found a difference in susceptibility of different races of rabbits to inoculation of cultures of spirochetes of syphilis, the short-eared albino being the most susceptible. The parenchyma of the testis was the most susceptible tissue into which an injection was made, as compared with the scrotum, prepuce, skin of the back and vaginal mucosa. Infected testes, conserved in the icebox, were infectious for five days. Infection was more certain during cold weather than during warm periods. Superinfections were difficult to secure with homologous strains, but were obtained in approximately 40 per cent with heterologous strains.

PAUL R. CANNON.

THE ACTION OF SLIGHTLY VIRULENT TUBERCLE BACILLI IN EXPERIMENTS WITH ANIMALS. P. UHLENHUTH and W. SEIFFERT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**:187, 1930.

Attenuated tubercle bacilli may cause extensive tuberculosis in susceptible guinea-pigs. In one instance, B C G regained full virulence for guinea-pigs and rabbits after a sojourn of one and one-half years in guinea-pigs.

THE INFLUENCE OF HEMATOTOXIC SUBSTANCES ON EXPERIMENTAL TUBERCULOSIS. H. SHIRAI, Jap. J. Exper. Med. **8**:457, 1930.

The factor causing anemia and the inhibitory influence on the tuberculous changes do not run parallel. Both hydroxylamine and glycerin cause an anemia, but they have no inhibitory influence on the tuberculous infection. Pyrodine causes an anemia and also shows a marked effect on the tuberculous change. The tuberculous change is not due to the anemia, but to the chemical nature of the substances. From these results and those of other workers, the inhibitory action seems to be due to the hydrazine group. Phenylhydrazine hydrochloric acid, methylphenylhydrazine and p-tolylhydrazine hydrochloric acid, as well as the substances mentioned, have the same effect on tuberculous infections and all have the hydrazine group as a common radical.

EDNA DELVES.

INFECTION OF B. ANTHRACIS THROUGH THE GUINEA-PIG'S MUCOUS MEMBRANE. K. KAGAYA, Jap. J. Exper. Med. **8**:489, 1930.

There is a marked difference in the relation of the skin and the mucous membranes to *B. anthracis*. Given orally, the organisms were found to penetrate the mesentery and reach one or two viscera in a short time. At the same time, a few bacilli were found in the small intestines. After three hours no organisms were found in the mesenteric glands or other viscera. Also the percentage of organisms was greater in the large intestines than in the small. After twenty-four hours, it was impossible to find any bacilli in the intestinal canal or the viscera.

EDNA DELVES.

Medicolegal Pathology

TRAUMA AND DEMENTIA PARALYTICA. J. V. KLAUDER and H. C. SOLOMON, J. A. M. A. **96**:1, 1931.

This article considers the medicolegal relations of trauma to dementia paralytica. Each case must be considered on its own merits with respect to: (1) the effect of trauma on intracranial contents, (2) the meaning of symptoms during the intercalary period and (3) the probable modification of the patient's usefulness and longevity. The relation of trauma to the localization of syphilitic lesions is discussed.

HISTOPATHOLOGY OF DIFFERENT TYPES OF ELECTRIC SHOCK ON MAMMALIAN BRAINS. L. R. MORRISON, A. WEEKS and S. COBB, J. Indust. Hyg. **12**: 324, 1930.

This article briefly reviews the literature as to the pathologic effect of electric shock on tissues, especially of the brain, and in addition clearly portrays the histologic changes in the brain following repeated sublethal shocks from a given quality and quantity of current. Rabbits, guinea-pigs and cats were used to illustrate the effect of carefully measured amounts of different kinds of current. From a histopathologic standpoint, in the cases in which repeated shocks were given with induction coil current, the dominant features in the brain were: hemorrhage, demyelinization, glial proliferation, excessive swelling and liquefaction

of the ganglion cells. Swelling of the oligodendroglia is one of the first signs even in cases in which a few shocks of three seconds' duration are given, death occurring in a few hours, or in those in which a single shock of from thirty to fifty seconds' duration is given, with almost immediate death. Pericapillary hemorrhage is another early sign. In older cases perivascular gliosis and demyelinated spots are seen. In animals shocked with a condenser discharge under the same conditions, which lived for from seven to seventy-two days, there were swelling and liquefaction of the ganglion cells and increased glial activity in the myelin, the ependyma and around the blood vessels, essentially the changes in shock induced by current from an induction coil. However, a limited perivascular necrosis was characteristic of this group. The series shocked with A-C current showed a greater tendency to hemorrhage, especially in the choroid plexus and the ventricles. Pericapillary extravasation of the blood, especially in the basal ganglions and the medulla, was more frequent, while lymphocytic infiltration of the pia and around the vessels was a prominent feature. Liquefaction of the ganglion cells was uncommon in the series shocked with A-current; the typical features were a greater tendency toward hemorrhage, shrinkage of the ganglion cells, a mild reaction of the glia and an absence of demyelinization. Under similar conditions, the series shocked with a condenser discharge showed swollen ganglion cells, as in the induction series, the glial reaction not being as severe. In this type the myelin is not broken down but shows vacuolization and mucoid degeneration, which is more severe than in any of the other forms.

C. G. WARNER.

TRAUMATIC ASPHYXIA. W. R. LAIRD and M. C. BORMAN, Surg. Gynec. Obst. **50**:578, 1930.

Although 138 cases of traumatic asphyxia have been reported heretofore in the medical literature, it is probable that the condition is more frequently found than the literature would indicate. Among the factors responsible for the morbidity of this condition are the occurrence of panics in large crowds, the collapse of large structures seating or housing large collections of people, human negligence and the desire for speed. The consequent use of machinery in industry and vehicles for rapid transportation have added materially to traumatic asphyxia. For the sake of accuracy and clarity, the authors suggest that the term traumatic asphyxia be applied to patients in whom there has been a squeezing compression of the chest and upper part of the abdomen with cessation of respiration for an abnormal length of time. They suggest that the local cyanosis occurring in an extremity following local trauma or pressure be called traumatic cyanosis, and that the rarely observed cyanosis occurring during an attack of grand mal epilepsy be termed epileptic cyanosis.

The typical syndrome described following traumatic asphyxia consists of cessation of respiration, with or without loss of consciousness; visual disturbances or blindness; extreme purplish cyanosis of the upper part of the trunk, the neck and the face, and subconjunctival hemorrhage. The invariable subconjunctival hemorrhage noted in this condition has a peculiar lozenge or wedge-shaped distribution, due to lack of supporting tissue. The cyanosis is probably essentially due to capillary and venous dilatation and engorgement as revealed by histologic studies. Multiple unsuspected fractures, especially of the thoracic vertebrae, may be associated and remain undetected, without roentgen examination. The probability of associated injuries to intrathoracic and abdominal viscera must always be remembered.

C. G. WARNER.

THE RELATION OF SURROUNDINGS AND TRAUMA TO DIABETES. F. UMBER, Klin. Wchnschr. **10**:5, 1931.

True insular diabetes does not result from psychic trauma; it results from physical trauma only when most of the pancreas has been destroyed. A psychic

or physical trauma may disclose a diabetic disposition or may aggravate an existing diabetes. These accentuations are usually insignificant.

EDWIN F. HIRSCH.

ACUTE DEGENERATIVE CHANGES IN AMMON'S HORN IN FRESH GUNSHOT WOUNDS OF THE BRAIN. K. NEUBÜRGER, Krankheitsforschung **7**:219, 1929.

In gunshot wounds of the brain, degenerative changes and necrosis occur in Ammon's horn owing to disturbances in the circulation. These changes occur early after the injury and appear to be due to a local anemia from vasoconstriction.

NECROSIS OF UTERUS FOLLOWING INJECTION OF SOAP POWDER. W. BICKENBACH, Med. Klin. **26**:1663, 1930.

Solution of soap powder was injected into the uterus to produce abortion. On account of peritonitis, laparotomy was performed and the uterus removed about twenty-four hours after the expulsion of a fetus of 3 months. The uterus and the tubes were found to be extremely necrotic, owing it is believed, to alkali hydroxides in the soap powder.

Technical

THE NEUTRAL RED TEST IN PERNICIOUS ANEMIA. S. J. COHEN, M. J. MATZNER and IRVING GRAY, Arch. Int. Med. **46**:979, 1930.

Three cases have been reported of patients with pernicious anemia in whom injected neutral red was recovered in the gastric extractions. Previous investigators have emphasized the diagnostic value of the neutral red test in pernicious anemia. Investigators have never before been able to recover neutral red in the gastric specimens in true pernicious anemia. The value of the test for neutral red is always questionable, because the presence of the dye in the stomach may be accounted for by regurgitation of the duodenal content. A simple and rapid method for the detection of neutral red in the gastric content is described. The presence of neutral red in the gastric extractions does not in itself exclude the diagnosis of pernicious anemia.

AUTHORS' SUMMARY.

THE CHOLESTEROL PARTITION OF THE BLOOD PLASMA IN PARENCHYMATOUS DISEASES OF THE LIVER. EMANUEL Z. EPSTEIN, Arch. Int. Med. **47**:82, 1931.

An added insight into the complex problem of the liver function seems to be gleaned from the determination of the total and cholesterol ester, a simple method that requires only from 1 to 2 cc. of blood plasma, and that can be repeated throughout the course of the disease. Ten cases of acute, diffuse, parenchymatous damage of the liver have been studied. The cholesterol ester values in the blood plasma were found to be diminished or entirely absent, corresponding with the severity of the disease process. With the improvement in the condition the ester values rose to their absolute and relative normal proportions. This progress as revealed by the ester values paralleled in large measure the general condition of the patient and the other liver function tests. In four cases of atrophic cirrhosis of the liver, with its slow evolution, slight damage and ample regeneration, the cholesterol partition was normal. The ester values seem to offer some means of diagnosing parenchymatous damage of the liver and, when repeated during the course of the disease, some prognostic significance.

AUTHOR'S SUMMARY.

THE MARCHI METHOD. DONALD DUNCAN, Arch. Neurol. & Psychiat. **25**:327, 1931.

Duncan studied the significance of so-called Elzholz bodies as brought out by the method of Marchi in human material, but especially in rats, dogs, rabbits and

cats. The bodies are minute particles of myelin that stain black or brown with osmic acid. They are situated between the myelin and the Schwann membrane or within the myelin and in the nodes of Ranvier. The Elzholz bodies are much in evidence in secondary (wallerian) as well as in so-called primary degeneration of the nerve. In the latter condition, the myelin is involved but the axon is spared. Duncan concludes that normal fibers always contain some black globules and irregular areas, and that the amount of Elzholz bodies depends on the technic of the Marchi method.

Fixation in formaldehyde, for instance, produces numerous artefacts, and for this reason the formaldehyde should be completely washed out in running water before the osmic acid mixture is used. The Bush modification (the mixture contains 1 part of osmic acid and 3 parts of sodium iodate in 300 parts of distilled water) is considered the best and most valuable method. Duncan does not consider the Marchi stain specific for wallerian degeneration. The strength of the osmic acid solution is of great importance in its application. GEORGE B. HASSIN.

A METHOD FOR THE DIFFERENTIAL STAINING OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA IN TISSUE SECTIONS. J. H. BROWN and LENA BRENN, Bull. Johns Hopkins Hosp. **48**:69, 1931.

The authors present the following method of differential staining: Stain paraffin sections in freshly filtered alum-hematoxylin (Harris) for from two to five minutes. Wash in acid alcohol (3 per cent hydrochloric acid in 95 per cent alcohol) until light pink. Wash in ammonia water (1 cc. of aqua ammoniae in 100 cc. of water) until blue. Wash in water and pour on the following mixture, staining for two minutes. In a small vial mix 5 drops of 5 per cent sodium bicarbonate containing 0.5 per cent phenol, with 0.75 cc. of a 1 per cent (by weight) aqueous solution of gentian violet. At this point it is better to proceed with one slide at a time. Wash quickly with water and cover with compound solution of iodine for one minute. Wash with water, blot and decolorize in 1 part ether plus 3 parts acetone; drop the solution on the slide until no more color comes off. Blot and stain with rosaniline hydrochloride (0.005 Gm. per hundred cubic centimeters of water) or basic fuchsin (0.1 cc. of saturated alcoholic solution per hundred cubic centimeters of water). Wash in water and blot, but do not allow the section to dry. Pass through acetone, decolorize and differentiate by dropping over the section a solution of 0.1 Gm. of picric acid in 100 cc. of acetone until the section becomes yellowish-pink. This is the most critical stage of the process and should be carried out by holding the slide over a white plate or dish. Most of the fuchsin should be decolorized from the tissue, but the gram-negative bacteria should remain red. Pass successively through acetone, equal parts of acetone and xylene and xylene. After clearing in xylene, mount in balsam.

EDNA DELVES.

A REAGENT FOR DEMONSTRATING FUNGI IN THE SKIN SCRAPINGS AND HAIR. T. CORNBLEET, J. A. M. A. **95**:1743, 1930.

Several drops of water are used to dissolve a relatively large quantity of sodium sulphide crystals. Equal parts of this solution and 95 per cent alcohol are mixed. A precipitate develops which redissolves as distilled water is added drop by drop. The reagent should be kept in a paraffin-coated, glass-stoppered bottle. The alcohol removes the oil at the surface of the keratin and between the layers of scales and also gives a refractive index that makes the structures more easily visible. The scales and hair should be soaked in ether to remove the oil at the surface. After the material has been placed on a slide under a cover glass, several drops of reagent are added. In several minutes, if the cover glass is gently tapped down, the clearing will occur more rapidly. Five or ten minutes are sufficient to obtain a satisfactory clearing. The microscopic picture is clear, and the vegetative structures are easily seen. EDNA DELVES.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 8, 1931

BALDUIN LUCKÉ, *President, in the Chair*

The William Wood Gerhard Gold Medal of the Philadelphia Pathological Society was awarded to Dr. Simon Flexner, director of the Rockefeller Institute for Medical Research, who addressed the Society on the subject, "Two Modern Plagues."

Regular Meeting, Feb. 12, 1931

CONGENITAL PULMONIC STENOSIS WITH UNUSUAL EXTRACARDIAC LESIONS. CHARLES-FRANCIS LONG.

During his youth the patient was a cross-country runner. He had a strenuous four years in the British army and was on his company's soccer and boxing teams. He emigrated to America at the age of 27, passing all examinations without comment. During the summer of his thirtieth year, his skin became suddenly blue after a bath in the ocean. This color would reappear whenever he became chilled or walked against the wind. At the age of 32, he was admitted to Medical Service B of the Episcopal Hospital, complaining of the bluish color, which had been present for five months, of edema of the ankles toward nightfall, which he had observed for three months, and of urgent dyspnea and vertigo, from which he had suffered for a week. The heart was moderately enlarged to the right. The rhythm was regular. There was a rasping systolic murmur, best heard in the third interspace to the left of the sternum; it radiated to both axillae and the angle of the left scapula. There was cyanosis of the capillary type. The liver was enlarged to the level of the umbilicus. There was moderate edema of the ankles. Microscopic examination of the capillaries of the nail bed showed them to be long, tortuous and sometimes with four loops filled. The oxygen saturation of the arterial blood was normal (94.6 per cent). The dextrose tolerance test showed that at the end of two hours the blood contained 260 mg. of sugar per hundred cubic centimeters, and that the urinary sugar was 1.1 per cent. The patient improved and was discharged in three weeks. During the next nine months, he was bedridden at home owing to a diarrhea which was thought to be a manifestation of colitis; there was evidence also of irritation of the cerebral and spinal motor pathways. There were periods of delirium, which would clear as suddenly as they had come. It was thought that the psychoneurologic manifestations might be evidence of a malignant endocarditis superimposed on a congenital lesion of the heart. He died in what might be described as a "typhoid state." The autopsy, as far as the heart was concerned, sustained the clinical diagnosis of congenital pulmonic stenosis. There was right ventricular preponderance. The valve measurements were: mitral, 8.5 cm.; tricuspid, 9 cm.; aortic, 6.4 cm.; pulmonary, 3.5 cm. A probe could pass through the foramen ovale, but in the opinion of the pathologist it was not functionally patent. No ductus arteriosus was seen.

The liver weighed 2,200 Gm., was firm, a mottled brown and studded throughout with yellow umbilicated lesions, which proved to be adenocarcinoma. The pancreas was normal in size and shape, but several large hard nodules in its head were due to adenocarcinoma. There were metastases to the periportal and mesenteric glands.

EXPERIMENTALLY PRODUCED LESIONS OF RHEUMATISM. V. H. MOON and HAROLD L. STEWART.

This article appeared in the February issue of the ARCHIVES, page 190.

HYPERPLASIA OF RAT AND MOUSE SKIN FROM SULPHYDRYL. STANLEY P. REIMANN.

Two points in the sulphydryl theory of growth by increase in number are not generally recognized. The first is that the sulphydryl group is the naturally occurring stimulus to cell division, and the second is that the chemical control of the well known balance between cell proliferation and its inhibition must be by way of a chemical equilibrium somewhat unique in its properties. As formulated by Hammett, reduced sulphur compounds stimulate mitosis and their semi-oxidized products inhibit this process.

To discover what would happen when sulphydryl compounds were applied to the normal intact skin, thiocresol in various concentrations and in various mediums was painted on the skins of rats and mice. As control, cresol in the same concentrations was used on the same animals on other parts. Hyperplasias involving the epithelial cells occurred on the parts treated with the sulphydryl compounds, whereas the parts treated with cresol remained normal. The details concerning the cellular differentiation and differential reactions between the epithelium and the underlying connective tissue will be published in detail by Hammett.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 9, 1931

JOSEPH A. CAPPS, *President, in the Chair*

VARIATION OF A BACILLUS COLI-LIKE ORGANISM. W. J. NUNGESTER and S. A. ANDERSON.

An organism recently isolated from empyema of the gallbladder was studied with the purpose of observing variations. By subjecting the purified original culture to conditions intended to produce variation or dissociation, variants were obtained differing from each other with respect to form of colony, fermentation of lactose, motility and agglutinability.

The change from the original form to that of the variants was effected with some difficulty, and we are unable to state the conditions that stimulate such changes, except in a general way. On the other hand, the reversion of the variants to the parent form was effected at will. Such conditions as aging on nutrient agar or a short passage through liquid medium was sufficient to accomplish reversion in certain variants. The presence of lactose was usually necessary to bring about the reversion of the forms that did not ferment lactose.

The ease with which variation occurs in liquid mediums is a source of error in determining the carbohydrate fermentation of variants under such conditions. More accurate information concerning the fermentation of carbohydrates by variants can be obtained on Andrade carbohydrate agar on which changes from one form to another are less likely to occur than in liquid mediums.

There was no correlation of the form of the colony with fermentation of lactose. Both S and R types of colony fermented lactose. On the other hand, similar forms of colony were encountered that failed to ferment lactose.

DISCUSSION

EDWIN F. HIRSCH: Since so much depends on purity of the bacterial strain in these studies of dissociation, were cultures prepared by the single-organism method?

W. J. NUNGESTER: We did not use the single-organism method because the results with such strains are the same as those with cultures purified in the usual manner.

UNDIFFERENTIATED ROUND CELL SARCOMA WITH SKELETAL SARCOMATOSIS (HEMACYTOBLASTOMA?). N. W. ROOME.

A round cell sarcoma of the ilium, with widespread skeletal, and few visceral, metastases, was reported. The patient had pain in the lower extremities, especially the left, for two years before admission, swelling in the region of the left ilium, loss of vision in the right eye and gradual loss of weight and strength. On the patient's admission to the University of Chicago Clinics a mass surrounding the left ilium and enlarged left inguinal glands were found. Roentgen examination disclosed increased thickness and density of the left ilium and of adjacent parts of the pubis and ischium. No other lesions were found at the first examination. There were moderate leukocytosis and anemia; the differential white blood cells count was approximately normal.

Treatment by Coley's toxins and x-rays resulted in slight improvement, but metastases rapidly spread into nearly all the bones of the body. The x-ray films of the skeletal metastases revealed diffuse widening of the medullary cavity, irregular changes in density of bone and slight periosteal formation of bone. There were a fluctuating fever and progressive anemia. Death occurred eight months after admission.

A huge tumor was found about the left ilium, ischium and pubis, filling the pelvis to the midline. When the tumor was cut into, the ilium was dense and thickened; the surrounding mass was coarsely trabeculated and only moderately firm, and was without bone or cartilage. The iliac lymph glands were infiltrated. All the other bones examined were massively infiltrated by tumor, causing little destruction of bone. There were tumor nodules in the pleurae, dura mater, spleen and pancreas.

The iliac tumor consisted of densely packed, irregularly arranged small "round cells" that appeared free in an irregular connective tissue stroma. In tissues treated by refixation in a solution of formaldehyde plus Zenker's solution and with Maximow's hematoxylin eosin-azure, most of the cells resembled the hemacytoblast (stem cell of the hematopoietic series) and a few cells contained neutrophil and eosinophil granules, suggesting myelocytes and premyelocytes. Most positively identified were several megakaryocytes. Certain cells with compact nuclei and acidophil cytoplasm suggested normoblasts. The cells of the metastases were less differentiated and resembled less the hemacytoblasts.

This tumor clinically resembles the "endothelial myeloma" of Ewing, but cytologically it is possibly hemacytoblastoma.

ANOMALIES OF INTESTINAL ROTATION. REPORT OF TWO CASES. H. E. HAYMOND.

The first anomaly was accidentally discovered during a surgical operation (Lester R. Dragstedt) in a man 68 years of age with carcinoma of the pylorus and of the greater curvature of the stomach. Owing to the abnormality a gastroenterostomy was not done, and resection was not attempted on account of widespread metastases. A further examination was made after death. All of the small bowel, with the exception of 8 cm. of terminal ileum, was behind a glistening membrane limited on the right side by the ascending colon anteriorly and the posterior parietal peritoneum posteriorly. The duodenum and the first part of the jejunum were in front of the superior mesenteric artery. The small intestine had

its own mesentery. This anomaly is best explained as a malrotation of the embryonic midgut in the second stage of rotation as described by Norman M. Dott. It occurred when the intestines returned to the peritoneal cavity from the normal developmental umbilical hernia and passed anterior to the superior mesenteric artery, thus forming a sac from the embryonic mesentery of the ascending, and the right half of the transverse colon.

The second patient with intestinal anomaly was a boy, aged 16 years, who had had intermittent attacks of severe vomiting since he was 2 days old. At operation (Lester R. Dragstedt) the cecum was found behind the stomach in the upper left quadrant, and the ascending colon and terminal ileum were wound around the base of a short mesenteric pedicle in such a manner as to produce obstruction of the upper part of the jejunum. At the operation a twist of the small intestine of 120 degrees was found and corrected, and the cecum was fixed in the right lower quadrant. The postoperative course was uneventful. Eleven and one-half months after operation, he had had no recurrence of symptoms and had gained approximately twenty pounds (9 Kg.) in weight. This anomaly is explained as an excessive rotation and abnormal fixation of a previous floating ileocecal segment of the embryonic midgut.

The complete report will be published in *Surgery, Gynecology and Obstetrics.*

THE COPPER, IRON AND ANTITRYPSIN CONTENTS OF POTENT EXTRACTS OF THE ROUS CHICKEN SARCOMA NO. 1. DAVID ROSBASH and ARTHUR LOCKE.

Freshly prepared extracts of Rous chicken sarcoma contain, on an average, 0.38 mg. of copper and 1.16 mg. of iron per gram of their nitrogen content, amounts nine times as large as those that characterize similarly prepared extracts of the pectoral muscles of control, nontumor-bearing hens. The metal-carrying fraction of the sarcoma extracts is concentrated, together with the tumor-inducing principle, by acid fractionation.

Saline extracts of the pectoral muscles of normal hens appear to be devoid of antitryptic potency. Similarly prepared extracts of Rous sarcoma tissue have an inhibiting action on trypsin approaching that of the blood serum in dilutions of equal nitrogen content. The antitryptic activity is concentrated, together with the copper content and the tumor-inducing principle, by acid fractionation.

Extracts of Rous sarcoma are not inactivated by cyanide. They behave, in this respect, like the "anaerobic" enzymes of the classification presented in a preceding paper. It is suggested that the "aerobic" enzymes of this classification, which are readily inactivated by cyanide, may be similarly inactivated by antitrypsin. Possibly the resistance to cyanide and the increased metal contents of the extracts of sarcoma indicate an increased anaerobic enzyme content, and the activity of the extracts may depend, in part, on their capacity (1) to suppress the aerobic processes, and (2) to supplement the anaerobic processes, of the cells contiguous to the area into which the injection has been made in such a way as to urge these cells gradually to convert into more wholly anaerobic, tumor cells.

CARCINOMA OF THE JEJUNUM. GEORGE MILLES.

Less than 200 carcinomas of the small intestine have been recorded. In large series of postmortem statistics, about 3 per cent of all carcinomas of the intestine have been found in the small bowel.

Like malignant growths elsewhere in the intestines, carcinomas of the small intestine manifest themselves clinically by obstruction and intussusception and by metastases, which in about half of the cases reported occurred early and almost entirely in the liver.

A Russian laborer, 33 years of age, noticed progressive loss of weight for a year and epigastric pain after meals for a month. One week after the onset of this pain, anorexia and vomiting increased his discomfort to such an extent that he sought relief in a hospital. During the month preceding admission he lost 20 pounds (9 Kg.) and during the entire year 43 (19.5 Kg.). A moderate

emaciation was noted, and a mass estimated to measure 6 cm. in diameter was palpated in the midepigastrium. There were 3,100,000 red blood cells per cubic millimeter of blood and 70 per cent hemoglobin, and the stomach fluids contained a total of 3 degrees of acid, but no free acid. The roentgen examination demonstrated an annular deformity of the pylorus. With a clinical diagnosis of carcinoma of the stomach, an operation was undertaken to relieve the obstruction. The liver was invaded by carcinomatous nodules, and the pylorus of the stomach was involved in a large mass which could not be resected. An anterior gastro-enterostomy was performed. The patient left the hospital after twelve days. He failed to recover his weight and strength, and the discomfort in the abdomen increased. After four months, vomiting became so marked that he was able to retain only small quantities of milk. He entered the Research and Educational Hospital of the University of Illinois, markedly emaciated, weak and pale. The abdomen protruded moderately and through the thin wall could be palpated the enlarged liver with its irregular, nodular edge and a separate mass in the right epigastrium. The hemoglobin was reduced to less than 20 per cent, and the red blood cells to 2,000,000 per cubic millimeter; there were many nucleated and irregular red cells. The leukocytes numbered 12,250 per cubic millimeter, of which 85 per cent were polymorphonuclear leukocytes. The gastric fluids contained 28 degrees of acid, but no free acid, and occasional traces of blood. Blood was found in the feces. The serum albumin was reduced to 2.59 per cent; the serum globulin was unchanged. Death occurred one month after admission and one and one-half years after the onset of symptoms. The peritoneal cavity contained 600 cc. of clear fluid. Opposite the healed abdominal incision were adhesions binding the intestines and the liver to the anterior abdominal wall. The liver weighed 5,230 Gm. and contained many umbilicated nodules, varying in color from tan to yellow, and as large as 3 cm. in diameter. The intervening liver substance was dark brown. The site of the gastro-enterostomy was obscured by surrounding adhesions, and the pylorus of the stomach, the duodenum, the jejunum and the medial half of the pancreas formed a mass which was disentangled with some difficulty. There was a thickening in the posterior wall of the jejunum close to the gastro-enterostomy. The stomach contained about 100 cc. of bile-stained fluid. The mucosa was pale, and both the pyloric orifice and the opening made by gastro-enterostomy were patent. About 1 cm. distal to the latter in the jejunum was a superficial raised ulceration, 3 cm. in diameter. Sections from this and from the liver presented adenocarcinoma. The failure to find carcinoma in the stomach or in the pancreas led to the conclusion that the mass in the jejunum was the primary adenocarcinoma. The tumor cells definitely resembled goblet cells.

Book Reviews

ANATOMIE UND PATHOLOGIE DER SPONTANERKRANKUNGEN DER KLEINEN LABORATORIUMSTIERE, KANINCHEN, MEERSCHWEINCHEN, RATTE, MAUS. Edited by RUDOLF JAFFÉ, Berlin. Price, 98 marks. Pp. 832, with 270 partly colored illustrations. Berlin: Julius Springer, 1931.

This book is the product of twenty-eight contributors who summarize what is known about the spontaneous diseases of the rabbit, guinea-pig, rat and mouse. The object of the work is (1) to assist the investigator working with these animals in determining whether conditions he may observe in them in the laboratory are the results of his experiments or are due to spontaneous diseases—an urgent problem that may arise at any time—and (2) to stimulate careful observation and study of the natural diseases of these animals on account of their inherent scientific interest as well as their bearing on experiments.

The vast amount of material on which the book is based has been gathered by laborious search of the literature as well as by systematic observations in various German institutes, particularly the Institut für Vererbungsforschung an der Landwirtschaftlichen Hochschule (Berlin-Dahlem), which has served as a depot for distributing material to the various contributors. That all recorded observations, often hidden in articles on other topics, have been included would be more than one can expect. And that the field of the book has been covered completely by the work that has been done up to this time is of course also out of question. But the book does meet the requirements that reasonably may be placed on a book of its kind at present. The hopes of the editor that in time the results of further work may warrant a new edition should receive encouragement.

The book is divided into two parts, special and general. The special part deals with the organs—it is essentially a pathologic anatomy—and covers 565 pages. By way of introduction to each organ system, the peculiarities in the normal anatomy of each species are described. The general part is devoted to the bacterial and parasitic diseases of the four species in question, carbohydrate metabolism and tumors. The bacterial and parasitic diseases are reviewed thoroughly. Chapters planned for the consideration of lipoid, mineral and pigment metabolism had to be omitted on account of lack of suitable material. The section on spontaneous tumors covers its field exhaustively, and the American work, notably that of Maude Slye, receives full and adequate attention. At the ends of the section are lists of references. The illustrations are satisfactory.

The book will be of help and interest to all who work scientifically with the rabbit, guinea-pig, mouse and rat. There is frequent need for a book like this in every laboratory where studies are made on these animals.

DIE GLOBULINE. By DR. MONA SPIEGEL-ADOLF. Volume IV. Handbuch der Kolloidwissenschaft. Edited by Prof. Wolfgang Ostwald. Price, 33 marks. Pp. 452. Dresden: Theodor Steinkopff, 1930.

The importance of the proteins as subjects for research in both the physical and the biologic sciences has resulted in a literature on proteins that is as varied as it is extensive. The task of collecting this literature, therefore, is extremely difficult since it carries the reader through many different types of journals ranging from theoretical chemistry and physics to clinical medicine. One consequently finds that practically all books on proteins tend to consider these important and interesting substances from the chemical and physicochemical points of view, and to ignore, or else dismiss with only a few meager references, the

important evidence bearing on the behavior and structure of protein obtained from immunologic studies. In the present volume, Dr. Spiegel-Adolf considers not only the chemical and physical but also the biologic and medical aspects of the subject. Her training in pathology and medicine, together with her extensive researches on the physical chemistry of the proteins, makes her especially fit to discuss these compounds from this comprehensive point of view. The result is a volume of great interest not only to colloid chemists but to physicians and biologists interested in following the important advances being made in the chemistry of protein.

Although this book deals with the globulins, and more specifically with the serum globulins and the vegetable globulin edestin, it contains many hundreds of references covering the entire field of the chemistry of proteins. Chapter 1, on the chemistry of the globulins, deals with the various kinds of globulins, their preparation and their chemical and physical properties. Chapters 2 and 3 deal with the reactions of globulins with alkalis and with acids. In chapter 4, the author discusses the solubilities of the globulins in neutral salt solutions and the chemical and physical properties of such solutions. Chapter 5 deals with the reactions of globulins with salts of heavy metals, inorganic colloids and such biologic colloids as the lipoids. Chapter 6, on globulins in biology and medicine, deals with quantitative methods for the determination of globulins, fluctuations of globulin content in health and in disease and immunologic properties of the globulins. The comprehensive manner in which the author has covered the field of the globulins together with the full and impartial discussion of the subjects presented makes this monograph invaluable to all who are interested in this class of proteins. It should also prove especially useful as a source of references to the older and important papers on the general chemistry of protein as well as to those dealing more specifically with the globulins themselves.

UEBER DAS PROBLEM DER BÖSARTIGEN GESCHWÜLSTE. EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG. By PROF. DR. LOTHAR HEIDENHAIN. Volume 2. Price, 42 marks. Pp. 207, with 229 illustrations. Berlin: Julius Springer, 1930.

Heidenhain, whose first volume on the same subject was reviewed in the ARCHIVES (**7**:378, 1929), affirms that carcinoma and sarcoma are always caused by a transmissible and infectious agent which is enclosed within the tumor cells. By a rather simple procedure of digestion of human neoplasms, given in detail in the previous review, he "frees" the agent from the malignant cells and the formless detritus resulting from the digestion containing the carcinogenic substance is then injected in small amounts into the thigh, the liver or the peritoneum of mice; this, Heidenhain asserts, leads to the inauguration of a new growth somewhere in the rodent's body.

Previous to Heidenhain's work no one was able to transfer cancer from man to animal. And, what is more, material freed from living malignant cells, as a rule, failed to induce a cancer in another animal of the same species.

The results presented by Heidenhain in no way disprove the "orthodox" teaching just mentioned. The percentage of the alleged positive results in his experiments is very small (about 7 in the first series and about 11 in the present volume), and it is most likely that the tumors in the mice are spontaneous, although Heidenhain quotes the names of a few German pathologists who informed him that spontaneous tumors are almost unheard of in the Teutonic mouse.

In brief, the present study by Heidenhain is no more than a continuation of that already published, since the same material and the same experimental methods were used. The monograph abounds in illustrations which together with the legends occupy 133 of 207 pages of the book. Unfortunately, the excellent plates are by no means a proof that the malignant condition found in the mice resulted from the inoculation of the "detritus." Moreover, the arguments brought forward by Heidenhain in defense of his thesis are rather unconvincing.

RECENT ADVANCES IN THE STUDY OF RHEUMATISM. By FREDERIC JOHN POYNTON, M.D., F.R.C.P. (LOND.); Physician, University College Hospital; Senior Physician, Hospital for Sick Children, Great Ormond Street, and BERNARD SCHLESINGER, M.A., M.D. (CAMB.), M.R.C.P. (LOND.); Physician to the Children's Department, Royal Northern Hospital; Physician to Outpatients, Hospital for Sick Children, Great Ormond Street. Price, $5.50. Pp. 313, with 25 illustrations. Philadelphia: P. Blakiston's Son & Company, 1931.

This book discusses the nomenclature, causation, morbid anatomy and treatment of "rheumatic diseases" in the light of recent developments. The first part deals with the nomenclature and the industrial aspects of the diseases. The second and largest part is devoted to "acute rheumatism," its causation, morbid anatomy, relation to tonsillitis, the allergic factor, electrocardiography and treatment. The rheumatism of childhood and the convalescent home treatment for rheumatic children receive detailed consideration. The third part deals with "chronic rheumatism"—bacteriologic investigations, morbid anatomy, metabolic changes, focal infection and treatment. The senior author is known in the history of the investigation of rheumatism for his bacteriologic researches in conjunction with Dr. Payne. The book gives a comprehensive and sympathetic picture of the results of the modern investigations of the nature of rheumatism. The recent American work receives full attention. The specific streptococcal theory, the multiple streptococcal theory, the allergic theory, the rôle of focal infection, the anatomic changes and other aspects of the rheumatic problems are subjected to judicial and helpful review. The book will appeal to all who are interested in the advancement of knowledge concerning the rheumatic infections.

AN INTRODUCTION TO PRACTICAL BACTERIOLOGY. A GUIDE TO BACTERIOLOGICAL LABORATORY WORK. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh, and J. E. MCCARTNEY, M.D., D.Sc. Third edition. Price, $3.50. Pp. 421. New York: William Wood & Company, 1931.

The first edition of this work appeared in 1925. The book was designed to set forth "as briefly as possible the essential methods and data relating to practical bacteriology." First come brief chapters on the biology of microbes, immunity in relation to bacteriology, the microscope, cultural and staining methods, animal inoculation, immunologic methods, water, milk and antiseptics. Chapters 9 to 23 deal with the characters of the disease-producing microbes and the diagnosis of infections by laboratory methods. There are no illustrations, except a few diagrams, no references and no discussion of the historical aspects of microbiology. There is inconsistency in that the proper names of microbic species occur now in ordinary type, now in italics. The book is a compact and up-to-date guide for the beginning worker in practical microbiology.

TEXT-BOOK OF GYNECOLOGY. By ARTHUR H. CURTIS, M.D., Professor and Head of the Department of Obstetrics and Gynecology, Northwestern University Medical School; Chief of the Gynecological Service, Passavant Memorial Hospital, Chicago. Cloth. Price, $5. Pp. 380, with 222 original illustrations. Philadelphia: W. B. Saunders Company, 1930.

Pathologists, especially those who are concerned with the pathologic anatomy and histology of the female genital organs, will be interested in this textbook. It embodies a refreshingly concise presentation, based on personal experience, "of all that the author believes is vital in [ciinical] gynecology." The illustrations are original, and it is to those of the microscopic appearances in various processes and the interpretation of them by the author that the attention of practical pathologists is directed especially. The author has a firm, firsthand grasp of general pathologic principles, and his gross and microscopic descriptions and illustrations are admirable. To the pathologist who must deal with gynecological material in the laboratory and often away from the clinic, this book will be of great help because it describes and illustrates, simply but adequately, the important morphologic appearances in their clinical setting.

Books Received

Società Internazionale di Microbiologia, Seziona Italiana. Atti del Secondo Congresso Nazionale di Microbiologia. Pp. 271. Milano: Istituto Sieroterapico Milanese, 1930.

Die sexuellen Zwischenstufen. Von Richard Goldschmidt, Dr. Phil. Nat. et Med.H.C., Professor und Direktor am Kaiser Wilhelm-Institut für Biologie in Berlin-Dahlem. Price, 45 marks; bound, 46.90 marks. Pp. 528, with 214 illustrations. Berlin: Julius Springer, 1931.

Abstracts of Theses. Science Series, volume 7, Ogden Graduate School of Science. Submitted to the Graduate Faculty of the University of Chicago for the Degree of Doctor of Philosophy, September, 1928—June, 1929. Pp. 484. Chicago: University of Chicago Press, 1931.

Recent Advances in Forensic Medicine. By Sydney Smith, M.D., M.R.C.P., D.P.H., Regius Professor of Forensic Medicine, University of Edinburgh, and John Glaister, Jr., M.D., D.Sc., J.P., Barrister-at-Law, Inner Temple; Professor of Forensic Medicine, The Medical Faculty, University of Egypt, Cairo, and Medico-Legal Consultant to the Egyptian Government. Price, $3.50. Pp. 194, with 66 illustrations. Philadelphia: P. Blakiston's Son & Company, 1931.

Report of the Medical Research Council for the Year 1929-1930. Price, 2 shillings, 6 pence. Pp. 138. London: His Majesty's Stationery Office, 1931.

. Diet and the Teeth: An Experimental Study. Part 2. A. Diet and Dental Disease. B. Diet and Dental Structure in Mammals Other Than the Dog. Medical Research Council, Special Report Series, no. 153. By May Mellanby. Price, 2 shillings, 6 pence. Pp. 93, with 28 illustrations. London: His Majesty's Stationery Office, 1930.

Iodine Supply and the Incidence of Endemic Goitre. Medical Research Council, Special Report Series, no. 154. By J. B. Orr. Price, 4 pence. Pp. 18. London: His Majesty's Stationery Office, 1931.

Undulant Fever with Special Reference to a Study of Brucella Infection in Iowa. National Institute of Health Bulletin, no. 158. By A. V. Hardy, C. F. Jordan, I. H. Borts and G. C. Hardy. Price, 25 cents. Pp. 89. Washington, D. C.: Government Printing Office, 1931.

Die Histogenese ekto-meso-dermaler Mischgeschwülste: Ein Beitrag zur Frage der Organisatorenwirkung (Spemann) beim pathologischen Wachstum. Von Prof. Dr. Paul Schürmann, Dr. med. Hans Pflüger und Zahnarzt Dr. Wilhelm Norrenbrock. Price, 11.50 marks. Pp. 94, with 79 illustrations. Leipzig: Georg Thieme, 1931.

A System of Bacteriology in Relation to Medicine. Medical Research Council. Volume 6 (Immunity). Cloth. Price, per volume, 1 pound, 1 shilling, net. London: His Majesty's Stationery Office, 1930. (May be obtained from the British Library of Information, 551 Fifth Avenue, New York.)

Text-Book of Pathology. By Robert Muir, M.A., M.D., Sc.D., LL.D., F.R.S., Professor of Pathology, University of Glasgow; Pathologist to the Western Infirmary, Glasgow. Price, $14. Pp. 872, with 501 figures. New York and Toronto: Longmans, Green & Company, 1930.

Studien über die Entstehung und den Verlauf der Lungenkrankheiten. Von Dr. N. Ph. Tendeloo, o. ö. Professor der allgemeinen Pathologie und der pathologischen Anatomie; Direktor des pathologischen Instituts der Reichsuniversität, Leiden. Zweite umgearbeitete und vermehrte Auflage. Paper. Price, 26 marks. Pp. 219, with 6 illustrations. Munich: J. F. Bergmann, 1931.

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